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Effects of Different Pressure Support Termination on Patient-Ventilator Synchrony

Evaluation of the Normal Inspiratory Flow-Volume Curve

REVIEWS—*PEDIATRIC ARDS (concluded)*

Surfactant in Pediatric Respiratory Failure

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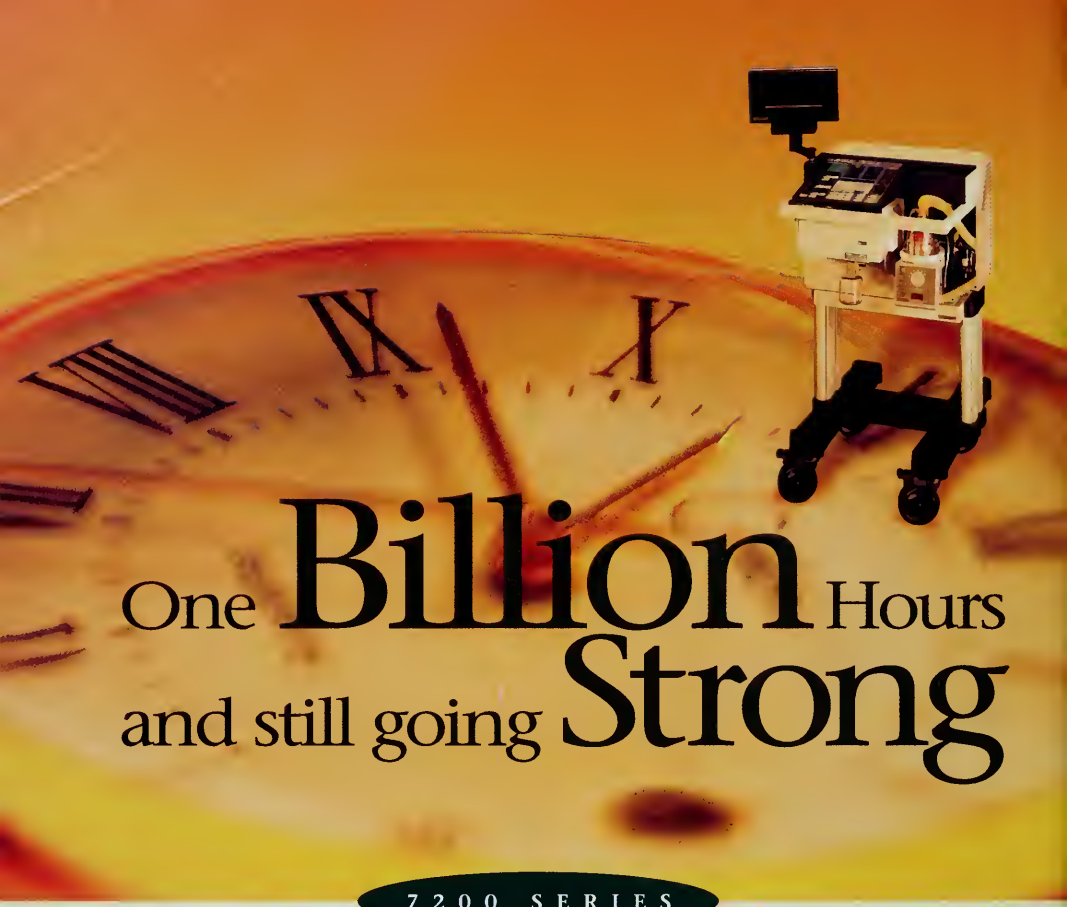

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RESPIRATORY CARE

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Established in 1956

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American Association for
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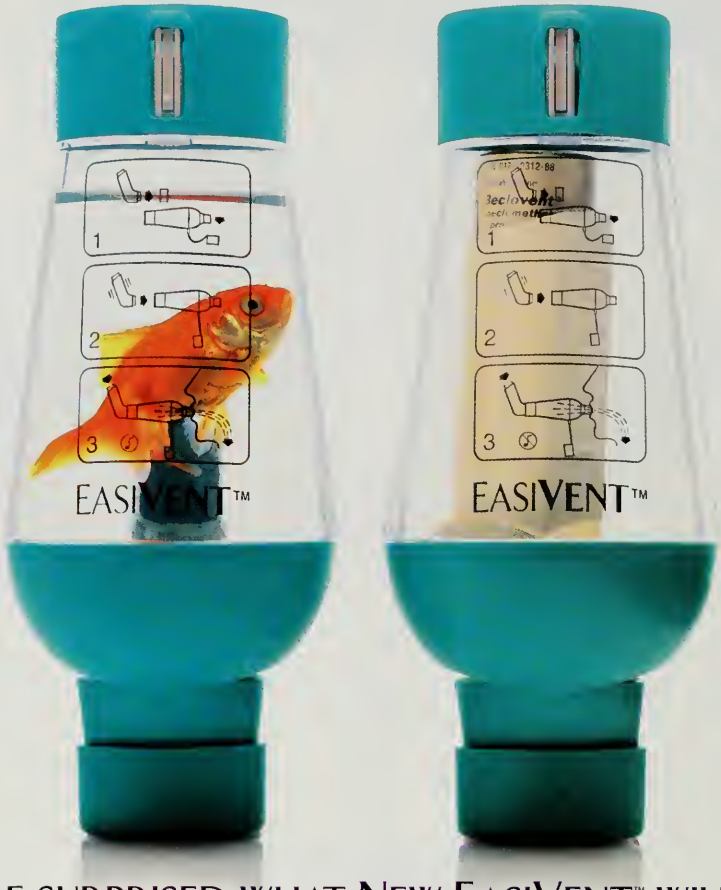

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Performance Testing New Peak Flow Meters—Pedersen OF, Miller MR, van der Mark TW. Eur Respir J 1998;12(2):261-262.

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Gastric Fluid Volume: Is It Really a Risk Factor for Pulmonary Aspiration?—Schreiner MS. Anesth Analg 1998;87(4):754-756.

Use of the Laryngeal Mask Airway As an Alternative to the Tracheal Tube during Ambulatory Anesthesia—Benumof JL. Anesth Analg 1998;87(4):977-978.

Use of a Lighted Stylet for Tracheal Intubation through the Intubating Laryngeal Mask—Asai T, Shingu K, Latto IP. Anesth Analg 1998;87(4):979.

Small Airways and Asthma: An Important Therapeutic Target? (review)—Howarth PH. Am J Respir Crit Care Med 1998;157(5 Pt 2):S173.

The Development of Large and Small Airways (review)—Jeffrey PK. Am J Respir Crit Care Med 1998;157(5 Pt 2):S174-S180.

Being More Positive about Negative Ventilation?—Wysocki M. Eur Respir J 1998;12(3):515-516.

Computer Tomographic Assessment of Perfluorocarbon and Gas Distribution during Partial Liquid Ventilation for Acute Respiratory Failure—Quintel M, Hirschl RB, Roth H, Loose R, van Ackern K. Am J Respir Crit Care Med 1998;158(1):249.

The average in vivo chest computed tomographic (CT) attenuation number (air = -1,000, soft tissue = 0, perflubron = +2,300 Hounsfield units [HU]) of 10 ventrodorsal-oriented lung segments was calculated to assess the distribution of gas and perflubron in 14 oleic acid lung-injured adult sheep during partial liquid ventilation (PLV, n = 7) or gas ventilation (GV, n = 7). Partial liquid ventilation was associated with a significant decrease in shunt fraction (PLV = 40 ± 12%, GV = 76 ± 12%, p = 0.004). Computed tomographic attenuation data during expiration (HUexp) demonstrated minimal gas aeration in GV animals in the dependent (segments 6–10) lung zones (HUexp = -562 ± 108 for segments 1–5, HUexp = -165 ± 104 for segments 6–10, p = 0.015). During PLV, perflubron was predominantly distributed to the dependent lung regions (HUexp = 579 ± 338 for segments 1–5, HUexp = 790 ± 149 for segments 6–10, p = 0.04). The ratio of the inspiratory to expiratory HU (HUinsp/exp) was greater in dependent than nondependent regions (mean HUinsp/exp segments 1–5 = 0.56, segments 6–10 = 0.81, p = 0.01), indicating that during inspiration relatively more gas than perflubron was distributed to the nondependent lung regions. We conclude that during PLV in this lung injury model, (1) gas exchange is improved when compared with gas ventilation, (2) perflubron is distributed predominantly to the dependent regions of the lung, and (3) although gas is distributed throughout the lung with each inspiration, more gas than perflubron goes to the nondependent lung regions.

Preflight versus en Route Success and Complications of Rapid Sequence Intubation in an Air Medical Service—Slater EA, Weiss SJ, Ernst AA, Haynes M. J Trauma 1998;45(3): 588.

BACKGROUND: Maintenance of an airway in the air medically transported patient is of paramount importance. The purpose of this study is to compare preflight versus en route rapid sequence intubation (RSI)-assisted intubations and to determine the value of air medical use of RSI. METHODS: This study is a 31-month retrospective review of all patients intubated and transported by a large city air medical service. Subgroup analysis was based on whether patients were transported from a hospital or a scene and whether they were intubated preflight or en route. Information on age, Glasgow Coma Scale score, type of scene, ground time, and previous attempts at intubation was recorded. Complica-

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tions included failures, multiple attempts at intubation, arrhythmias, and need for repeated paralytic agents. Comparisons were made using a confidence interval analysis. An alpha of 0.05 was considered significant; Bonferroni correction was used for multiple comparisons. RESULTS: Three hundred twenty-five patients were intubated and transported by Lifeflight during the study period. Two hundred eighty-eight patients were intubated using RSI (89%). The success rate was 97%. Preflight intubations were performed on 100 hospital calls and 86 scene calls. En route intubations were performed on 40 hospital cases and 62 scene calls. Patients who underwent preflight intubations were significantly younger than those who underwent en route intubations for both the hospital group (34 ± 11 vs. 44 ± 24 years, $p < 0.05$) and the scene group (27 ± 13 vs. 32 ± 16 years,$p < 0.05$). Otherwise, the demographic characteristics of the four groups were similar. Trauma accounted for 60 to 70% of hospital transfers and almost 95 to 100% of scene calls. Compared with preflight intubations, there was a significant decrease in ground time for hospital patients who were intubated en route (26 ± 10 vs. 34 ± 11 minutes, $p < 0.05$) and for scene patients who were intubated en route (11 ± 8 vs. 18 ± 9 minutes, $p < 0.05$). There were no significant differences between the groups for number of failures (9 of 288), arrhythmias (18 of 288), or necessity for repeated paralysis (8 of 288). Multiple intubation attempts were performed in more scene preflight patients (30 of 86, 35%) than scene en route patients (16 of 62, 26%), but this did not reach statistical significance. Even for patients having previous attempts at intubation, the success rate using RSI was 93% (62 of 67). CONCLUSION: Air medical intubations, both preflight and en route, for both scene calls and interhospital transports, can be done with a very high success rate. Rapid sequence intubation may improve the success rate. For scene calls, there was a significant decrease in ground time, and there was a trend toward fewer multiple intubation attempts when the patient was intubated en route instead of preflight.

Abdominal Compartment Syndrome (review)—Saggi BH, Sugerman HJ, Ivatury RR, Bloomfield GL. J Trauma 1998;45(3):597.

The ACS is a clinical entity that develops from progressive, acute increases in IAP and affects multiple organ systems in a graded fashion because of differential susceptibilities. The gut is the organ most sensitive to IAH, and it develops evidence of end-organ damage before the development of the classic renal, pulmonary, and cardiovascular signs. Intracranial derangements with ACS are now well described. Treatment involves expedient decompression of the abdomen, without which the syndrome of end-organ damage and reduced oxygen delivery may lead to the development of multiple organ failure and, ultimately, death. Multiple trauma, massive hemorrhage, or protracted operation with massive volume resuscitation are the situations in which the ACS is most frequently encountered. Knowledge of the ACS, however, is also essential for the management of critically ill pediatric patients (especially those with AWD) and in understanding the limitations of laparoscopy. The role of IAH in the pathogenesis of NEC, central obesity co-morbidities, and pre-eclampsia/eclampsia remains to be fully studied.

Negative Pressure Ventilation versus Conventional Mechanical Ventilation in the Treatment of Acute Respiratory Failure in COPD Patients—Corrado A, Gorini M, Giananni R, Pelagatti C, Villella G, Buoncristiano U, et al. Eur Respir J 1998;12(3):519.

This case-control study was aimed to evaluate the effectiveness of negative pressure ventilation (NPV) versus conventional mechanical ventilation (CMV) for the treatment of acute respiratory failure (ARF) in patients with chronic obstructive pulmonary disease (COPD) admitted to a respiratory intermediate intensive care unit (RIICU) and four general intensive care units (ICU). Twenty-six COPD patients in ARF admitted in 1994-95 to RIICU and treated with NPV (cases) were matched according to age (± 5 yrs), sex, causes triggering ARF, Acute Physiology and Chronic Health Evaluation (APACHE) II score (± 5 points), pH (±0.05) and arterial carbon dioxide tension ($PaCO_2$) on admission with 26 patients admitted to ICU and treated with CMV (controls). The primary end points of the study were inhospital death for both groups and the need for endotracheal intubation for cases. The secondary endpoints were length and complications of mechanical ventilation and length of hospital stay. The effectiveness of matching was 91%. Mortality rate was 23% for cases and 27% for controls (NS), five cases needed endotracheal intubation, four of whom subsequently died. The duration of ventilation in survivors was significantly lower in cases than in controls, with a median of 16 h (range 2-111) versus 96 h (range 12-336) ($p < 0.02$), whereas the length of hospital stay was similar in the two groups, with a median of 12 days (range 2-47) for cases vs 12 days (range 3-43) (NS) for controls. No complications were observed in cases, whereas three controls developed infective complications. These results suggest that negative pressure ventilation is as efficacious as conventional mechanical ventilation for the treatment of acute respiratory failure in patients with chronic obstructive pulmonary disease and that it is associated with a shorter duration of ventilation and a similar length of hospital stay compared with conventional mechanical ventilation.

Influence of Acute Lung Volume Change on Contractile Properties of Human Diaphragm—Polkey MI, Hamnegard CH, Hughes PD, Rafferty GF, Green M, Moxham J. J Appl Physiol 1998;85(4):1322.

The effect of stimulus frequency on the in vivo pressure generating capacity of the human diaphragm is unknown at lung volumes other than functional residual capacity. The transdiaphragmatic pressure (Pdi) produced by a pair of phrenic nerve stimuli may be viewed as the sum of the Pdi elicited by the first (T1 Pdi) and second (T2 Pdi) stimuli. We used bilateral anterior supramaximal magnetic phrenic nerve stimulation and a digital subtraction technique to obtain the T2 Pdi at interstimulus intervals of 999, 100, 50, 33, and 10 ms in eight normal subjects at lung volumes between residual volume and total lung capacity. The reduction in T2 Pdi that we observed as lung volume increased was greatest at long interstimulus intervals, whereas the T2 Pdi obtained with short interstimulus intervals remained relatively stable over the 50% of vital capacity around functional residual capacity. For all interstimulus intervals, the total pressure produced by the pair decreased as a function of increasing lung volume. These data demonstrate that, in the human diaphragm, hyperinflation has a disproportionately severe effect on the summation of pressure responses elicited by low-frequency stimulations; this effect is distinct from and additional to the known length-tension relationship.

Expiratory Flow Limitation and Intrinsic Positive End-Expiratory Pressure in Obesity—Pankow W, Podszus T, Gutheil T, Penzel T, Peter J, Von Wichert P. J Appl Physiol 1998; 85(4):1236.

Breathing at very low lung volumes might be affected by decreased expiratory airflow and air trapping. Our purpose was to detect expiratory flow limitation (EFL) and, as a consequence, intrinsic positive end-expiratory pressure (PEEPi) in grossly obese subjects (OS). Eight OS with a mean body mass index (BMI) of 44 ± 5 kg/m2 and six age-matched normal-weight control subjects (CS) were studied in different body positions. Negative expiratory pressure (NEP) was used to determine EFL. In contrast to CS, EFL was found in two of eight OS in the upright position and in seven of eight OS in the supine position. Dynamic PEEPi and mean transdiaphragmatic pressure (mean Pdi) were measured in all six CS and in six of eight OS. In OS, PEEPi increased from 0.14 ± 0.06 (SD) kPa in the upright position to 0.41 ± 0.11 kPa in the supine position ($p < 0.05$) and decreased to 0.20 ± 0.08 kPa in the right lateral position ($p < 0.05$, compared with supine), whereas, in CS, PEEPi was significantly smaller (<0.05 kPa) in each position. In OS, mean Pdi

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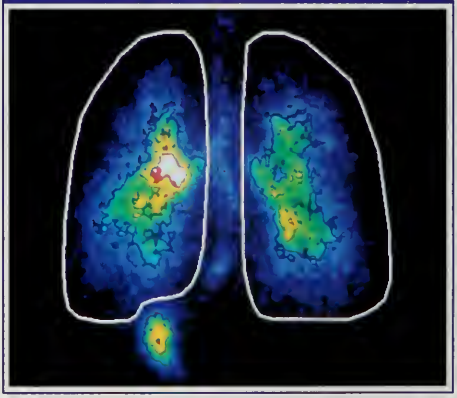

Scintigraph showing the deposition pattern of ^{99m}Tc-labeled budesonide inhaled from Turbuhaler®

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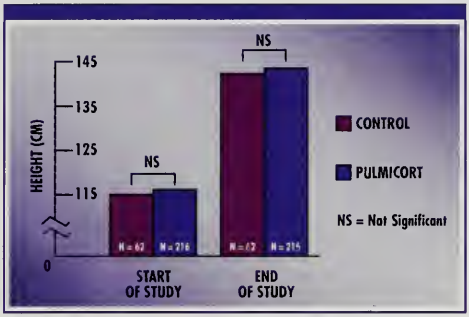

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† Recommended pediatric starting dose is 1 inhalation of 200 mcg, twice daily.

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WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to PULMICORT TURBUHALER because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although PULMICORT TURBUHALER may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Transfer of patients from systemic corticosteroid therapy to PULMICORT TURBUHALER may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, and eczema

Patients who are on drugs which suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible pediatric patients or adults on immunosuppressant doses of corticosteroids. In pediatric or adult patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package insert for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered

PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma

As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If bronchospasm occurs following dosing with PULMICORT TURBUHALER, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with PULMICORT TURBUHALER should be discontinued and alternate therapy instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma not responsive to their usual doses of bronchodilators occur during treatment with PULMICORT TURBUHALER. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS

General: During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

PULMICORT TURBUHALER will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of PULMICORT TURBUHALER in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing PULMICORT TURBUHALER.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, PULMICORT TURBUHALER should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of all pediatric patients taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression (see PRECAUTIONS, Pediatric Use section)

Although patients in clinical trials have received PULMICORT TURBUHALER on a continuous basis for periods of 1 to 2 years, the long-term local and systemic effects of PULMICORT TURBUHALER in human subjects are not completely known. In particular, the effects resulting from chronic use of PULMICORT TURBUHALER on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown

In clinical trials with PULMICORT TURBUHALER, localized infections with Candida albicans occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with PULMICORT TURBUHALER therapy, but at times therapy with PULMICORT TURBUHALER may need to be temporarily interrupted under close medical supervision.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral or parasitic infections, or ocular herpes simplex

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids

Drug Interactions: In clinical studies, concurrent administration of budesonide and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. Ketoconazole, a potent inhibitor of cytochrome P450 3A, may increase plasma levels of budesonide during concomitant dosing. The clinical significance of concomitant administration of ketoconazole with PULMICORT TURBUHALER is not known, but caution may be warranted.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies were conducted in mice and rats using oral administration to evaluate the carcinogenic potential of budesonide

There was no evidence of a carcinogenic effect when budesonide was administered orally for 91 weeks to mice at doses up to 200 mcg/kg/day (approximately $\frac{1}{2}$ the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis).

In a 104-week oral study in Sprague-Dawley rats, a statistically significant increase in the incidence of gliomas was observed in male rats receiving an oral dose of 50 mcg/kg/day (approximately $\frac{1}{2}$ the maximum recommended daily inhalation dose on a mcg/m^2 basis), no such changes were seen in male rats receiving oral doses of 10 and 25 mcg/kg/day (approximately $\frac{1}{10}$ and $\frac{1}{4}$, the maximum recommended daily inhalation dose on a mcg/m^2 basis) or in female rats at oral doses up to 50 mcg/kg/day (approximately $\frac{1}{4}$, the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Two additional 104-week carcinogenicity studies have been performed with oral budesonide at doses of 50 mcg/kg/day (approximately $\frac{1}{2}$ the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis) in male Sprague-Dawley and Fischer rats. These studies did not demonstrate an increased glioma incidence in budesonide-treated animals as compared with concurrent controls or reference corticosteroid-treated groups (prednisolone and triamcinolone acetonide). Compared with concurrent controls, a statistically significant increase in the incidence of hepatocellular tumors was observed in all three steroid groups (budesonide, prednisolone, triamcinolone acetonide) in these studies.

The mutagenic potential of budesonide was evaluated in six different test systems. Ames Salmonella/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in Drosophila melanogaster, and DNA repair analysis in rat hepatocyte culture. Budesonide was not mutagenic or clastogenic in any of these tests.

The effect of subcutaneous budesonide on fertility and general reproductive performance was studied in rats. At 70 mcg/kg/day (approximately $\frac{1}{2}$ the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis), decreases in maternal body weight gain, prenatal viability and viability of the young at birth and during lactation were observed. No such effects were noted at 5 mcg/kg (approximately $\frac{1}{20}$, the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

Pregnancy: Teratogenic Effects: Pregnancy Category C. As with other glucocorticoids, budesonide produced fetal loss, decreased pup weight and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day in rabbits (approximately $\frac{1}{2}$ the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) and 500 mcg/kg/day in rats (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

No teratogenic or embryocidal effects were observed in rats when budesonide was administered by inhalation at doses up to 250 mcg/kg/day (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: Corticosteroids are secreted in human milk. Because of the potential for adverse reactions in nursing infants from any corticosteroid, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Actual data for budesonide are lacking.

Pediatric Use: Safety and effectiveness of PULMICORT TURBUHALER in pediatric patients below 6 years of age have not been established.

In pediatric asthma patients the frequency of adverse events observed with PULMICORT TURBUHALER was similar between the 6- to 12-year age group (N=172) compared with the 13- to 17-year age group (N=124).

Oral corticosteroids have been shown to cause growth suppression in pediatric and adolescent patients, particularly with higher doses over extended periods. If a pediatric or adolescent patient on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered (see PRECAUTIONS).

Geriatric Use: One hundred patients 65 years or older were included in the US and non-US controlled clinical trials of PULMICORT TURBUHALER. There were no differences in the safety and efficacy of the drug compared to those seen in younger patients.

ADVERSE REACTIONS

The following adverse reactions were reported in patients treated with PULMICORT TURBUHALER.

The incidence of common adverse events is based upon double-blind, placebo-controlled US clinical trials in which 1,116 adult and pediatric patients age 6-70 years (472 females and 644 males) were treated with PULMICORT TURBUHALER (200 to 800 mcg twice daily for 12 to 20 weeks) or placebo.

The following table shows the incidence of adverse events in patients previously receiving bronchodilators and/or inhaled corticosteroids in US controlled clinical trials. This population included 232 male and 62 female pediatric patients (age 6 to 17 years) and 332 male and 331 female adult patients (age 18 years and greater).

Adverse Events with ≥ 3% Incidence reported by Patients on PULMICORT TURBUHALER

Adverse Event	Placebo N=284 %	PULMICORT TURBUHALER 200 mcg twice daily N=286 %	400 mcg twice daily N=289 %	800 mcg twice daily N=98 %
Respiratory System				
Respiratory infection	17	20	24	19
Pharyngitis	9	10	9	5
Sinusitis	7	11	7	2
Voice alteration	0	1	2	6
Body As A Whole				
Headache	7	14	13	14
Flu syndrome	6	6	6	14
Pain	2	5	5	5
Back pain	1	2	3	6
Fever	2	2	4	0
Digestive System				
Oral candidiasis	2	2	4	4
Dyspepsia	2	1	2	4
Gastroenteritis	1	1	2	3
Nausea	2	2	1	3
Average Duration of Exposure (days)	59	79	80	80

The table above includes all events (whether considered drug-related or non drug-related by the investigators) that occurred at a rate of ≥3% in any one PULMICORT TURBUHALER group and were more common than in the placebo group. In considering these data, the increased average duration of exposure for PULMICORT TURBUHALER patients should be taken into account.

The following other adverse events occurred in these clinical trials using PULMICORT TURBUHALER with an incidence of 1% to 3% and were more common on PULMICORT TURBUHALER than on placebo:

- Body As A Whole - neck pain
- Digestive - abdominal pain, dry mouth, vomiting
- Musculoskeletal - fracture, myalgia
- Platelet, Bleeding and Clotting - ecchymosis
- Resistance Mechanisms - infection
- Cardiovascular - syncope
- Metabolic and Nutritional - weight gain
- Nervous - hypertonia, migraine
- Psychiatric - insomnia
- Special Senses - taste perversion

In a 20-week trial in adult asthmatics who previously required oral corticosteroids, the effects of PULMICORT TURBUHALER 400 mcg twice daily (N=53) and 800 mcg twice daily (N=53) were compared with placebo (N=53) on the frequency of reported adverse events. Adverse events, whether considered drug-related or non drug-related by the investigators, reported in more than five patients in the PULMICORT TURBUHALER group and which occurred more frequently with PULMICORT TURBUHALER than placebo are shown below (% PULMICORT TURBUHALER and % placebo). In considering these data, the increased average duration of exposure for PULMICORT TURBUHALER patients (78 days for PULMICORT TURBUHALER vs 41 days for placebo) should be taken into account.

Body As A Whole	asthenia (9% and 2%)	Digestive	dyspepsia (8% and 0%)
	headache (12% and 2%)		nausea (6% and 0%)
	pain (10% and 2%)		oral candidiasis (10% and 0%)
Musculoskeletal	arthralgia (6% and 0%)	Respiratory	cough increased (6% and 2%)
			respiratory infection (32% and 13%)
			rhinitis (6% and 2%)
			sinusitis (16% and 11%)

Patients Receiving PULMICORT TURBUHALER Once Daily

The adverse event profile of once-daily administration of PULMICORT TURBUHALER 200 mcg and 400 mcg, and placebo, was evaluated in 309 adult asthmatic patients in an 18-week study. The study population included both patients previously treated with inhaled corticosteroids, and patients not previously receiving corticosteroid therapy. There was no clinically relevant difference in the pattern of adverse events following once-daily administration of PULMICORT TURBUHALER when compared to twice-daily dosing.

Pediatric Studies: In a 12-week placebo-controlled trial in 404 pediatric patients 6 to 18 years of age previously maintained on inhaled corticosteroids, the frequency of adverse events for each age category (6 to 12 years, 13 to 18 years) was comparable for PULMICORT TURBUHALER (at 100, 200 and 400 mcg twice daily) and placebo. There were no clinically relevant differences in the pattern or severity of adverse events in children compared with those reported in adults.

Adverse Event Reports From Other Sources: Rare adverse events reported in the published literature or from marketing experience include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and bronchospasm; symptoms of hypocorticism and hypercorticism, psychiatric symptoms including depression, aggressive reactions, irritability, anxiety and psychosis.

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in each position was significantly larger compared with CS. Mean Pdi increased from 1.02 ± 0.32 kPa in the upright position to 1.26 ± 0.17 kPa in the supine position (not significant) and decreased to 1.06 ± 0.26 kPa in the right lateral position ($p < 0.05$, compared with supine), whereas there were no significant changes in CS. We conclude that in OS 1) tidal breathing can be affected by EFL and PEEPi; 2) EFL and PEEPi are promoted by the supine posture; and 3) the increased diaphragmatic load in the supine position is, in part, related to PEEPi.

Effect of Prolonged, Heavy Exercise on Pulmonary Gas Exchange in Athletes—Hopkins SR, Gavin TP, Siafakas NM, Haseler LJ, Olfert IM, Wagner H, Wagner PD. J Appl Physiol 1998;85(4):1523.

During maximal exercise, ventilation-perfusion inequality increases, especially in athletes. The mechanism remains speculative. We hypothesized that, if interstitial pulmonary edema is involved, prolonged exercise would result in increasing ventilation-perfusion inequality over time by exposing the pulmonary vascular bed to high pressures for a long duration. The response to short-term exercise was first characterized in six male athletes [maximal O_2 uptake (VO_2 max) = 63 mL · kg $^{-1}$ · min $^{-1}$] by using 5 min of cycling exercise at 30, 65, and 90% VO_2 max. Multiple inert-gas, blood-gas, hemodynamic, metabolic rate, and ventilatory data were obtained. Resting log SD of the perfusion distribution (log SDQ) was normal [0.50 ± 0.03 (SE)] and increased with exercise (log SDQ = 0.65 ± 0.04, $p < 0.005$), alveolar-arterial O_2 difference increased (to 24 ± 3 Torr), and end-capillary pulmonary diffusion limitation occurred at 90% VO_2 max. The subjects recovered for 30 min, then, after resting measurements were taken, exercised for 60 min at approximately 65% VO_2 max. O_2 uptake, ventilation, cardiac output, and alveolar-arterial O_2 difference were unchanged after the first 5 min of this test, but log SDQ increased from 0.59 ± 0.03 at 5 min to 0.66 ± 0.05 at 60 min ($p < 0.05$), without pulmonary diffusion limitation. Log SDQ was negatively related to total lung capacity normalized for body surface area ($r = -0.97$, $p < 0.005$ at 60 min). These data are compatible with interstitial edema as a mechanism and suggest that lung size is an important determinant of the efficiency of gas exchange during exercise.

Percutaneous Dilatational Tracheostomy—Early Results and Long-Term Outcome of 326 Critically Ill Patients—Walz MK, Peitgen K, Thurauf N, Trost HA, Wolfhard U, Sander A, et al. Intensive Care Med 1998;24(7):685.

OBJECTIVE: To analyze perioperative and postoperative complications and long-term sequelae following percutaneous dilatational tracheostomy (PDT). DESIGN: A prospective clinical study of patients undergoing PDT. SETTING: Seven intensive care units at a University hospital PATIENTS: 326 intensive care patients (202 male, 124 female; age: 11-95 years) with indications for tracheostomy. INTERVENTIONS: Using tracheoscopic guidance, 337 PDTs were performed according to Ciaglias' method. In 106 decannulated patients, tracheal narrowing was assessed by plain tracheal radiography. RESULTS: Two procedure-related deaths were seen (0.6%). Perioperative and postoperative complications occurred with 9.5% of the PDTs. One of 106 patients, who were followed-up for at least 6 months, showed a clinically relevant tracheal stenosis. Subclinical tracheal stenosis of at least 10% of the cross-sectioned area was recognized in 46 of 106 patients (43.4%). In the univariate analysis, the degree of stenosis was influenced by the age of the patient ($p = 0.044$), the duration of intubation prior to PDT ($p = 0.042$) and by the duration of cannulation ($p = 0.006$). These parameters had no statistical significance in a multiple regression model. CONCLUSION: When performed by experienced physicians, percutaneous dilatational tracheostomy under fiberoptic guidance is a safe method. The risks of early complications and of clinically relevant tracheal stenoses are low. Subclinical tracheal stenoses are found in about 40% of patients following PDT.

Acute Hypoxemic Respiratory Failure in Children: Case Mix and the Utility of Respiratory Severity Indices—Peters MJ, Tasker RC, Kiff KM, Yates R, Hatch DJ. Intensive Care Med 1998;24(7):699.

OBJECTIVE: Acute hypoxemic respiratory failure (AHRF) is a common reason for emergency pediatric intensive care. An objective assessment of disease severity from acute physiological parameters would be of value in clinical practice and in the design of clinical trials. We hypothesised that there was a difference in the best early respiratory indices in those who died compared with those who survived. DESIGN: A prospective observational study of 118 consecutive AHRF admissions with data analysis incorporating all blood gases. SETTING: A pediatric intensive care unit in a national children's hospital. INTERVENTIONS: None. RESULTS: Mortality was 26/118, 22% (95% confidence interval 18-26%). There were no significant differences in the best alveolar-arterial oxygen tension gradient (A-aDO_2, torr), oxygenation index (OI), ventilation index (VI), or P_{aO_2}/F_{IO_2} during the first 2 days of intensive care between the survivors and non-survivors. Only the mean airway pressure (MAP, cm H_2O) used for supportive care was significantly different on days 0 and 1 ($p < 0.05$) with higher pressure being used in non-survivors. Multiple logistic regression analysis did not identify any gas exchange or ventilator parameter independently associated with mortality. Rather, all deaths were associated with coincident pathology or multi-organ system failure, or perceived treatment futility due to pre-existing diagnoses instead of unsupportable respiratory failure. When using previously published predictors of outcome (VI > 40 and OI > 40; A-aDO_2 > 450 for 24 h; A-aDO_2 > 470 or MAP > 23; or A-aDO_2 > 420) the risk of mortality was overestimated significantly in the current population. CONCLUSION: The original hypothesis was refuted. It appears that the outcome of AHRF in present day pediatric critical care is principally related to the severity of associated pathology and now no longer solely to the severity of respiratory failure. Further studies in larger series are needed to confirm these findings.

Declining Severity Adjusted Mortality: Evidence of Improving Neonatal Intensive Care—Richardson DK, Gray JE, Gortmaker SL, Goldmann DA, Pursley DM, McCormick MC. Pediatrics 1998;102(4 Pt 1):893.

Objectives. Declines in neonatal mortality have been attributed to neonatal intensive care. An alternative to the 'better care' hypothesis is the 'better babies' hypothesis; ie, very low birth weight infants are delivered less ill and therefore have better survival. Design. We ascertained outcomes of all live births <1500 g in two prospective inception cohorts. We estimated mortality risk from birth weight and illness severity on admission and measured therapeutic intensity. We calculated logistic regression models to estimate the changing odds of mortality between cohorts. Patients and Setting. Two cohorts in the same two hospitals, 5 years apart (1989-1990 and 1994-1995) (total n = 739). Results. Neonatal intensive care unit mortality declined from 17.1% to 9.5%, and total mortality declined from 31.6% to 18.4%. Cohort 2 had lower risk (higher birth weight, gestational age, and Apgar scores and lower admission illness severity for newborns ≥ 750 g). Risk-adjusted mortality declined (odds ratio, 0.52; confidence interval, 0.29-0.96). One third of the decline was attributable to 'better babies' and two thirds to 'better care.' Use of surfactant, mechanical ventilation, and pressors became more aggressive, but decreases in monitoring, procedures, and transfusions resulted in little change in therapeutic intensity. Conclusions. Mortality decreased nearly 50% for infants <1500 g in 5 years. One third of this decline is attributable to improved condition on admission that reflects improving obstetric and delivery room care. Two thirds of the decline is attributable to more effective newborn intensive care, which was associated with greater aggressiveness of respiratory and cardiovascular treatments. Attribution of improved birth

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weight specific mortality solely to neonatal intensive care may underestimate the contribution of high-risk obstetric care in providing 'better babies.'

Measurement of Overinflation by Multiple Linear Regression Analysis in Patients with Acute Lung Injury—Bersten AD. Eur Respir J 1998;12(3):526.

Strategies to optimize alveolar recruitment and prevent lung overinflation are central to ventilatory management of patients with acute lung injury (ALI). The recent description of overinflation using multilinear regression analysis of airway pressure (Paw) and flow (V) data allows a functional assessment of lung mechanics. However, this technique has not been studied in ALI patients. During 15 positive end-expiratory pressure (PEEP) trials in 10 ALI patients, respiratory elastance was partitioned into volume-independent (E1) and volume-dependent ($E2V_T$) components, where $Paw = (E1 + E2V_T)V + RrsV + Po$; where V is volume, V_T is tidal volume, Rrs is respiratory resistance and Po is static recoil pressure at end-expiration (equivalent to total PEEP). Then, %E2 was calculated as $(100E2V_T)/(E1 + E2V_T)$; a measure of lung overinflation when %E2 > 30%. Alveolar recruitment, assessed as a PEEP-induced increase in V > 50 mL at a constant Paw occurred in 14 of 15 trials (299±34 mL, mean ± SEM), but was independent of the degree of lung inflation. Lung overinflation was common (six of 15 clinically set PEEP levels) and occurred despite a dynamic elastic distending pressure (Pel,dyn) < 30 cm H_2O during 18 of 36 PEEP titrations. During a PEEP titration the resultant %E2 was directly related to delta-(peak airway pressure-Po) ($r_s = 0.86$, $p < 0.001$) and delta(Pel,dyn-Po) ($r_s = 0.89$, $p < 0.001$). The 95% predictive intervals for a 2 cm H_2O change in either driving pressure were %E2 values of 30.4-68.1% and 32.8-69.2%, respectively. Single or continuous measurement of %E2 (a measure of lung inflation) is a readily available method for titrating ventilatory parameters. Further, during a positive end-expiratory pressure titration a change in ventilatory driving pressure > or =2 cm H_2O is indicative of overinflation.

Comprehensive Analysis of Risk Factors for Acquisition of *Pseudomonas Aeruginosa* in Young Children with Cystic Fibrosis—Kosorok MR, Jalaluddin M, Farrell PM, Shen G, Colby CE, Laxova A, et al. Pediatr Pulmonol 1998;26(2):81.

The objective of this study was to identify risk factors of significance for acquisition of *Pseudomonas aeruginosa* by children with cystic fibrosis (CF). Our working hypothesis is that exposure of infants and young children with CF to older, infected patients increases their risk for acquiring this organism. A special opportunity arose to study this question in detail, as we have been performing a randomized clinical trial of neonatal screening for CF throughout the state of Wisconsin during the period of 1985-1994. Patients were selected for this study based on either early identification through screening or diagnosis by standard methods. A longitudinal protocol employed at Wisconsin's two CF Centers includes routine cultures of respiratory secretions and collection of clinical, demographic, and activity information on patients and their families. Previous observations in our trial revealed that one center at an old hospital in an urban location showed a significantly shorter time to acquisition of *P. aeruginosa* for CF patients followed there. To study the center effect further, we performed statistical analyses using survival curves and stepwise regression analysis of all life history covariates available. The results of these analyses showed that the statistically significant correlations involve the following risk factors: 1) center and old hospital ($r = 0.42$); 2) center and original physician ($r = 0.61$); 3) center and exposure to pseudomonas-positive patients ($r = 0.29$); and 4) population density and urban location ($r = 0.49$). The final statistical model demonstrated that increased risk due to aerosol use (odds ratio = 3.45, $p = 0.014$) and a protective effect associated with education of the mother (odds ratio = 0.81, $p = 0.024$) were the most significant factors for acquisition of P. aeruginosa. The previously observed center effect was confined to the 1985-1990 interval at the old hospital (odds ratio = 4.43, $p < 0.001$). We conclude that multiple factors are involved in increasing the risk of young children with CF to acquire *P. aeruginosa*, and that the observed center effect can best be explained by a combination of factors. These results suggest that facilities and methods used to care for young children with CF can significantly influence their likelihood of acquiring pseudomonas in the respiratory tract.

Efficacy of Curosurf in a Rat Model of Acute Respiratory Distress Syndrome—van Helden HP, Kuijpers WC, Langerwerf PE, Langen RC, Haagsman HP, Bruijnzeel PL. Eur Respir J 1998; 12(3):533.

Curosurf, a natural lung surfactant, is considered a potential candidate for improving the treatment of acute respiratory distress syndrome (ARDS). To investigate this in a rat model of early-stage ARDS, Curosurf (62.5, 125 or 250 mg x kg^{-1}) was administered by intratracheal bolus at 10 or 24 h following an intratracheal lipopolysaccharide (LPS; 1.6 mg x kg^{-1}) challenge. Survival, respiratory frequency (fR), lung wet weight (LWW), total protein and cell differentiation in bronchoalveolar lavage fluid (BALF) were assessed. Curosurf treatment at 10 h after LPS challenge resulted in 100% survival at both 62.5 and 125 mg x kg^{-1}; at a dose of 250 mg x kg^{-1} administered at 10 h after LPS, 1 out of 6 animals died. At a dose of 125 mg x kg^{-1} Curosurf administered at 24 h after LPS, 1 out of 6 animals died. In contrast, only 35% of animals survived when not treated with Curosurf. Curosurf treatment resulted in an improved fR and in a significantly decreased LWW, total protein and number of polymorphonuclear cells in BALF. In conclusion, Curosurf treatment improved respiratory frequency and decreased mortality, pulmonary oedema and inflammation. As the decreased mortality was observed in spontaneously breathing nonoxygenated animals, the results cannot be extrapolated to human artificially ventilated acute respiratory distress syndrome patients with the expectation of a decreased mortality. The results suggest, however, that Curosurf may be an important therapeutic measure in early-stage acute respiratory distress syndrome.

One-Year Follow-Up of Young Children Hospitalized for Wheezing: the Influence of Early Anti-Inflammatory Therapy and Risk Factors for Subsequent Wheezing and Asthma—Reijonen TM, Korppi M. Pediatr Pulmonol 1998;26(2):113.

We investigated the 1-year outcome of children hospitalized for wheezing, paying special attention to the effect of early anti-inflammatory therapy. In addition, we identified risk factors for recurrent wheezing and asthma. Eighty-eight children under 2 years old treated in the hospital for wheezing were followed for 1 year. Nebulized anti-inflammatory therapy was given for 16 weeks: 31 patients received budesonide, 29 patients cromolyn sodium, and 28 control patients received no therapy. The number of subsequent physician-diagnosed wheezing episodes was recorded. Four months of anti-inflammatory therapy did not significantly decrease the occurrence of asthma 1 year later: 45% of patients in the cromolyn group, 42% in the budesonide group, and 61% in the control group had asthma, defined as at least two bronchial obstruction episodes during the 1-year period after the original hospitalization for wheezing. An age over 12 months at the time of the initial bronchial obstructing episode [$p = 0.009$, risk ratio (RR) = 5.4, 95% confidence interval (CI) = 1.53-19.31], failure to identify a viral cause ($p = 0.0003$, RR = 12.0, CI = 3.16-45.40), history of wheezing ($p = 0.02$, RR = 14.6, CI = 1.59-132.10), the presence of atopy ($p = 0.01$, RR = 5.3, CI = 1.47-19.21), a family history of atopy ($p = 0.03$, RR = 3.6, CI = 1.15-11.12), and serum eosinophil cationic protein (ECP) > or = 16 microg/L ($p = 0.005$) were significant risk factors for asthma. We conclude that early anti-inflammatory therapy for 4 months does not significantly decrease the occurrence of asthma during the period of 1 year following hospitalization for the original epi-

sode of wheezing. Young children requiring hospital admission for wheezing during a respiratory tract infection are at increased risk of having subsequent asthma if they have wheezed previously, if they have atopy or a family history of atopy, if they have elevated serum ECP, if they are over 12 months of age at the original bronchial obstructive episode, and especially when viral studies are negative.

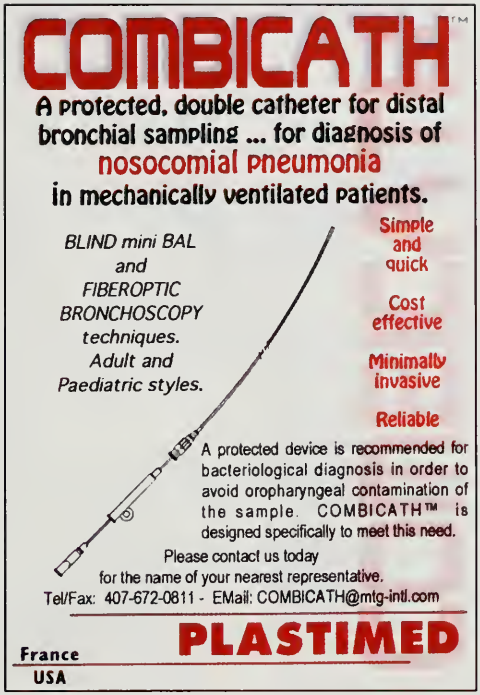
Ventilation Index and Outcome in Children with Acute Respiratory Distress Syndrome—Paret G, Ziv T, Barzilai A, Ben-Abraham R, Vardi A, Manisterski Y, Barzilay Z. Pediatr Pulmonol 1998;26(2):125.

The purpose of this investigation was to determine the predictive value of the ventilation index (VI) in children with acute respiratory distress syndrome (ARDS). We performed a 10-year retrospective chart review of children who were admitted to the Pediatric Intensive Care Unit with a diagnosis of ARDS. Acute respiratory distress syndrome was defined as acute onset of diffuse, bilateral pulmonary infiltrates of noncardiac origin, and severe hypoxemia, defined as the ratio of the arterial partial pressure of oxygen to the fraction of inspired oxygen of <200 and a positive end expiratory pressure of 6 cm H_2O or greater. Records of daily arterial blood gas results and ventilator settings were reviewed, and the ventilation index (VI=partial pressure of arterial CO_2 x peak airway pressure x respiratory rate/1,000) was calculated each time the measurements were made. These values were correlated with outcome (survival or nonsurvival). The VI was not different at the time of diagnosis of ARDS in the patients who lived, compared with those who subsequently died. However, by 3 to 5 days after study entry, the VI of nonsurvivors was significantly higher than for survivors ($p < 0.05$). The VI for survivors remained between 30 and 35 throughout the study period, whereas the VI of nonsurvivors continued to increase with time. A VI of >65 predicted death with a specificity and positive predictive value of >90% on days 3 through 9. We conclude that the VI provides a reliable prognostic marker in children with ARDS, and its increase above 65 indicates a need for orderly intervention with alternative modalities of care.

A Comparison of Three Modes of Ventilation with the Use of an Adult Circle System in an Infant Lung Model—Tobin MJ, Stevenson GW, Horn BJ, Chen EH, Hall SC, Cote CJ. Anesth Analg 1998;87(4):766.

We examined the efficiency of an adult circle system with adult bellows to deliver minute ventilation (VE) to an infant test lung model. A Narkomed 2B system (North American Dräger, Telford, PA) using three modes of ventilator setup were used: A = time-cycled, volume-controlled using bellows excursion to control delivered volume; B = time-cycled, pressure-controlled using inspiratory pressure limit adjustment to control delivered volume; C = time-cycled, pressure-controlled using the inspiratory flow adjustment to control delivered volume. VE was measured with two compliances (normal and low) and four endotracheal tube (ETT) sizes (2.5-, 3.0-, 3.5-, and 4.0-mm inner diameter). VE was measured at peak inspiratory pressures (PIP) of 20, 30, 40 or 50 cm H_2O while respiratory rate (RR) was held constant at 20 breaths/min. VE was measured as RR was set at 20, 30, 40, or 50 breaths/min while target PIP was held constant at 20 cm H_2O. Data were analyzed using the multiple regression technique. With the low compliance model, VE was nearly identical regardless of the ventilator setup. With the normal compliance model, minor differences in VE were observed, especially at the highest RR and PIP. VE was dependent on RR, PIP, and lung compliance. Overall, the ventilator setup resulted in minor changes in VE. Very high PIPs were required to deliver VE to the low compliance model. ETT size did not affect VE when lung compliance was low; however, smaller ETT size was a factor when test lung compliance was normal, decreasing delivered VE at higher PIP and RR. We conclude that with a Narkomed 2B adult circle system VE is dependent on PIP, RR, and lung compliance, but not on mode of ventilator setup. IMPLICATIONS: The results of this laboratory investigation indicate that when an adult circle system is used during infant anesthesia, the ventilation delivered depends primarily on the respiratory rate, peak inspiratory pressure, and the compliance of the lung being ventilated, rather than on the specific mode of ventilator setup.

Individual Use of Antiasthmatic Drugs in the European Community Respiratory Health Survey—Janson C, Chinn S, Jarvis D, Burney P. Eur Respir J 1998;12(3):557.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A previous analysis of drug utilization in the European Community Respiratory Health Survey found that only between 8 and 29% of subjects with asthma-related symptoms were using antiasthmatic medication in the different areas studied. The aim of this analysis was to investigate which variables were related to individual use of antiasthmatic medication in different geographical areas. Thirty-three centres in 14 countries were analysed, in which a total of 16,854 people (52.1% females, mean age 33.8 yrs, range 20-48) underwent a structured interview, measurement of specific immunoglobin E, spirometry and methacholine challenge test. The use of antiasthmatic drugs in individuals was, in most countries, independently related to asthma-related respiratory symptoms, bronchial hyperresponsiveness (BHR) and atopy. In all countries smokers with respiratory symptoms were less likely to be using antiasthmatic drugs than nonsmokers and exsmokers. In four of 14 countries females were significantly more likely to use antiasthmatic medication than males, while age and socioeconomic status were unrelated to medication. The use of inhaled anti-inflammatory drugs was positively related to symptoms, BHR and atopy and negatively related to current smoking. In conclusion, in many countries smokers were less likely to be using antiasthmatic drugs than were nonsmokers with comparable levels of symptoms and bronchial hyperresponsiveness. Age and socioeconomic status were unrelated to medication, while in some countries females were more likely than males to use antiasthmatic medication.

A Comparison of the Disposable versus the Reusable Laryngeal Mask Airway in Paralyzed Adult Patients—Brimacombe J, Keller C, Morris R, Mecklem D. Anesth Analg 1998; 87(4):921.

A disposable (polyvinyl chloride) laryngeal mask airway (LMA) with dimensions identical to, but physical properties different from (stiffer tube/thicker cuff), the reusable (silicone) LMA has recently become available. We performed a randomized, cross-over study of 60 paralyzed, anesthetized patients to test the hypothesis that the use of these devices was different in terms of ease of insertion, airway sealing pressure, fiberoptic position, and changes in intracuff pressure during N_2O anesthesia. We also tested the hypothesis that the airway sealing pressure of the LMA is suboptimal if the cuff is inflated to a high intracuff pressure. Both the devices were inserted into each patient in random order, and their performance was assessed at two intracuff pressures (60 and 180 cm H_2O) by a blind observer. Subsequently, intracuff pressures were measured during N_2O anesthesia for the second device. Ease of insertion was similar; there was no difference in first attempt success rates (97% vs 98%) and insertion times (15 vs 13 s) for the disposable and reusable LMA, respectively. There were no differences in airway sealing pressure or fiberoptic position. Airway sealing pressure was significantly higher at 60 cm H_2O intracuff pressure compared with the airway sealing pressure at 180 cm H_2O for both devices ($p < 0.02$). During N_2O anesthesia, the intracuff pressure remained stable for the disposable LMA but increased significantly for the reusable LMA. We conclude that the disposable and reusable LMAs perform similarly in paralyzed adult patients, but that the disposable LMA has more stable intracuff pressures during N_2O anesthesia. Inflation of the LMA to high intracuff pressures produces a suboptimal seal. IMPLICATIONS: This randomized, single-blind, within-patient study of 60 adult patients shows that the disposable (polyvinyl chloride) and reusable (silicone) laryngeal mask airways perform similarly, but that the disposable laryngeal mask airway has more stable intracuff pressures during N_2O anesthesia. Inflation of either device to high intracuff pressures produces a suboptimal seal.

Jet Ventilation in Upper Airway Obstruction: Description and Model Lung Testing of a New Jetting Device—Garry B, Woo P, Perrault DF Jr, Shapshay SM, Wurm WH. Anesth Analg 1998;87(4):915.

Patients with critical upper airway stenosis require a tracheotomy for corrective surgery. We describe a new transtracheal device that permits safe ventilation of these patients without tracheotomy. It is based on a coaxial bicannular design that allows 'push-pull' ventilation by jetting gas through the inner cannula and applying suction through the outer cannula. It further allows monitoring of airway pressure, tidal volume, and end-tidal CO_2. The device was placed in the 'trachea' of an artificial lung, and the preparation was made airtight by sealing the proximal end of the trachea. Tidal volumes and their associated pressures were measured simultaneously at different parts of the airway at several lung compliances and airway resistance settings while varying the jet and suction pressures. A large range of tidal volumes was achieved at safe airway pressures using clinically relevant airway resistance and lung compliance settings. Airway pressures measured through the device correlated well with pressures measured directly in the airways at the same time. Tidal volumes, measured through a Wright respirometer in the suction line, exceeded actual values at high suction settings and decreased below actual values at low suction settings. This new form of jet ventilation allowed efficient ventilation of the artificial lung with a totally occluded upper airway. IMPLICATIONS: Tracheotomy is required for surgery to relieve stridor because gas forced into the trachea at high pressures through a percutaneously placed needle (jetting) cannot be exhaled quickly enough for respiration. We describe a device that allows jetting in the stridorous patient by actively assisting expiration, thereby eliminating the tracheotomy requirement.

Characteristics of Asthma in the Elderly—Weiner P, Magadle R, Waizman J, Weiner M, Rabner M, Zamir D. Eur Respir J 1998;12(3): 564.

Asthma occurs more frequently in the elderly than is usually appreciated and may, therefore, be underdiagnosed and undertreated. This study evaluated the relationship between asthma symptoms and the degree of airflow obstruction in elderly and young asthmatics. Fifteen young asthmatics (<65 yrs) (group A), 15 aged >65 yrs with onset of symptoms before 65 yrs (group B), and 15 aged >65 yrs with onset of symptoms after 65 yrs (group C), were studied. Patients used daily diary cards, during 2 weeks, to record inhaled β2-agonist consumption and severity of asthma symptoms. Long-standing asthma was associated with a significantly lower forced expiratory volume in one second as compared with recent onset asthma. The asthma-symptom score was highest in group A, lower in group B and significantly lower in group C. When symptoms were related to the degree of obstruction (asthma index), it was higher in the young asthmatics than in both groups of elderly patients. In conclusion, elderly patients with long-standing asthma had more severe airway obstruction than patients with recently acquired disease. Older patients particularly those with long-standing disease complained less about asthma symptoms. Within the various groups of patients, subjective symptoms of asthma were negatively related to asthma duration.

A Comparison of Active and Simulated Chiropractic Manipulation as Adjunctive Treatment for Childhood Asthma—Balon J, Aker PD, Crowther ER, Danielson C, Cox PG, O'Shaughnessy D, et al. N Engl J Med 1998; 339(15):1013.

BACKGROUND: Chiropractic spinal manipulation has been reported to be of benefit in nonmusculoskeletal conditions, including asthma. METHODS: We conducted a randomized, controlled trial of chiropractic spinal manipulation for children with mild or moderate asthma. After a three-week base-line evaluation period, 91 children who had continuing symptoms of asthma despite usual medical therapy were randomly assigned to receive either active or simulated chiropractic manipulation for four months. None had previously received chiropractic care. Each subject was treated by 1 of 11 participating chiropractors, selected by the family according to location. The primary outcome measure was the change from base line in the peak expiratory flow, measured in the morning, before the use of a bronchodilator, at two

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and four months. Except for the treating chiropractor and one investigator (who was not involved in assessing outcomes), all participants remained fully blinded to treatment assignment throughout the study. RESULTS: Eighty children (38 in the active-treatment group and 42 in the simulated-treatment group) had outcome data that could be evaluated. There were small increases (7 to 12 liters per minute) in peak expiratory flow in the morning and the evening in both treatment groups, with no significant differences between the groups in the degree of change from base line (morning peak expiratory flow, $p=0.49$ at two months and $p=0.82$ at four months). Symptoms of asthma and use of 3-agonists decreased and the quality of life increased in both groups, with no significant differences between the groups. There were no significant changes in spirometric measurements or airway responsiveness. CONCLUSIONS: In children with mild or moderate asthma, the addition of chiropractic spinal manipulation to usual medical care provided no benefit.

Effect of Nebulized Ipratropium on the Hospitalization Rates of Children with Asthma—Qureshi F, Pestian J, Davis P, Zaritsky A. N Engl J Med 1998;339(15):1030.

BACKGROUND: Anticholinergic medications such as ipratropium improve the pulmonary function of patients with acute exacerbations of asthma, but their effect on hospitalization rates is uncertain. METHODS: We conducted a randomized, double-blind, placebo-controlled study of 434 children (2 to 18 years old) who had acute exacerbations of moderate or severe asthma treated in the emergency department. All the children received a nebulized solution of albuterol (2.5 or 5 mg per dose, depending on body weight) every 20 minutes for three doses and then as needed. A corticosteroid (2 mg of prednisone or prednisolone per kilogram of body weight) was given orally with the second dose of albuterol. Children in the treatment group received 500 microg (2.5 ml) of ipratropium bromide with the second and third doses of albuterol; children in the control group received 2.5 mL of normal saline at these times. RESULTS: Overall, the rate of hospitalization was lower in the ipratropium group (59 of 215 children [27.4 percent]) than in the control group (80 of 219 [36.5 percent], $p=0.05$). For patients with moderate asthma (indicated by a peak expiratory flow rate of 50 to 70 percent of the predicted value or an asthma score of 8 to 11 on a 15-point scale), hospitalization rates were similar in the two groups (ipratropium: 8 of 79 children [10.1 percent]; control: 9 of 84 [10.7 percent]). For patients with severe asthma (defined as a peak expiratory flow rate of <50 percent of the predicted value or an asthma score of 12 to 15), the addition of ipratropium significantly reduced the need for hospitalization (51 of 136 children [37.5 percent], as compared with 71 of 135 [52.6 percent] in the control group; $p=0.02$). CONCLUSIONS: Among children with a severe exacerbation of asthma, the addition of ipratropium bromide to albuterol and corticosteroid therapy significantly decreases the hospitalization rate.

Tracking of Lung Function Parameters and the Longitudinal Relationship with Lifestyle—Twisk JW, Staal BJ, Brinkman MN, Kemper HC, van Mechelen W. Eur Respir J 1998;12(3):627.

The purpose of this study was to analyse tracking (i.e. relative stability over time/predictability of future values by early measurements) of lung function parameters and their longitudinal relationship with lifestyle (smoking, alcohol consumption, daily physical activity, neuromotor and cardiopulmonary fitness, and dietary intake of retinol and polyunsaturated fatty acids (PUFA)). Data were obtained from the observational Amsterdam Growth and Health Study, a longitudinal study with six repeated measurements between ages 13-27 yrs ($n=167$). The statistical analyses were carried out with generalized estimating equations. The following 'stability' coefficients were found: for forced vital capacity (FVC) in males 0.66 (95% confidence interval (CI): 0.54-0.77) and in females

0.51 (95% CI: 0.43-0.60); for forced expiratory volume in one second (FEV_1) in males 0.65 (95% CI: 0.50-0.80), in females 0.53 (95% CI 0.46-0.60); for peak expiratory flow (PEF) in both males and females 0.41 (95% CI: 0.31-0.51). Positive relationships were found between alcohol consumption and FVC and FEV_1 and between neuromotor fitness and PEF and (only for males) with FVC and FEV_1. Physical activity was inversely related to PEF and the intake of PUFA positively related to FVC and FEV_1. Smoking was related to a decrease in FVC and FEV_1; changes in physical activity positively correlated to changes in FVC. In conclusion, high to moderate stability/tracking was observed for forced vital capacity and forced expiratory volume in one second; for peak expiratory flow it was slightly lower. Preventive strategies regarding improvements of lung function should focus on smoking cessation and improving daily physical activity.

Time to Peak Tidal Expiratory Flow and the Neuromuscular Control of Expiration—van der Ent CK, van der Grinten CP, Meessen NE, Luijendijk SC, Mulder PG, Bogaard JM. Eur Respir J 1998;12(3):646.

The ratio of the time needed to reach peak tidal expiratory flow (tPTEF) and the duration of expiration (tE) is used to detect airflow obstruction in young children. tPTEF is decreased in patients with asthma, but knowledge about the physiological determinants of this parameter is scarce. This study examined the relationship between tPTEF and postinspiratory activities of inspiratory muscles and evaluated the effects of changing sensory information from the lung. Airflow patterns and electromyographic (EMG) activity of inspiratory muscles were recorded in seven spontaneously breathing, anaesthetized cats. The trachea was cannulated and, as a result, the larynx and upper airways were bypassed. Changes in postinspiratory muscle activity were induced by changing afferent sensory nerve information (by cooling the vagus nerves, by administration of histamine and by additional application of continuous positive airway pressure (CPAP)). Durations of postinspiratory activities of the diaphragm and intercostal muscles (characterized by their time constants tau diaphr and tau interc) correlated strongly with tPTEF (r=0.85 and 0.77, respectively). Tau diaphr, tau interc and tPTEF were significantly increased during cooling of the vagus nerves (4-8 degrees C) compared with values at 22 and 37 degrees C ($p<0.05$). Conversely, administration of histamine and CPAP caused significant decreases in tau diaphr, tau interc and tPTEF, which were absent during cooling of the vagus nerves. In conclusion, the time needed to reach peak tidal expiratory flow is highly influenced by the activities of inspiratory muscles during the early phase of expiration which, in turn, depend on the activities of vagal receptors in the lung.

Mouth Occlusion Pressure, CO_2 Response and Hypercapnia in Severe Chronic Obstructive Pulmonary Disease—Montes de Oca M, Celli BR. Eur Respir J 1998;12(3):666.

The resting mouth occlusion pressure 0.1 s after onset of inspiration (P0.1) and minute ventilation ($\dot{V}E$) and their response to CO_2 in patients with chronic obstructive pulmonary disease (COPD) remain controversial. The ventilatory drive and the factors that predict resting arterial CO_2 tension (Pa,CO_2) were studied in 19 eucapnic and 14 hypercapnic severe COPD patients, and 20 controls. The CO_2 response was evaluated by the Read technique. The $\dot{V}E$, and P0.1 as a function of end-tidal CO_2 tension (Pet,CO_2) was used to study the ventilatory ($\Delta\dot{V}E/\Delta Pet,CO_2$) and P0.1 response ($\Delta P0.1/\Delta Pet,CO_2$). In the patients, respiratory muscle function and pleural occlusion pressure 0.1 s after onset of inspiration (Ppl,0.1) were evaluated with simultaneous measurement of pleural (Ppl) and gastric (Pga) pressures. Hypercapnic patients had lower forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and arterial O_2 tension (Pa,O_2). Resting P0.1 was higher in patients than in controls, whereas $\Delta P0.1/\Delta Pet,CO_2$ was similar in the three groups. There was no difference in resting P0.1 (3.6±2.0 versus 4.3±2.8 kPa (2.7±1.5 versus 3.2±2.1 cm H_2O), $p=0.2$) and Ppl,0.1 (1.4±2.3 versus 5.2±3.3 kPa (4.08±1.7 versus 3.9±2.5 cm H_2O), $p=0.22$) between eucapnic and hypercapnic COPD, whereas $\Delta\dot{V}E/\Delta Pet,CO_2$ was lower in the hypercapnic group (0.29±0.24 versus 0.66±0.5 L x min(-1) x kPa, $p<0.001$). By logistic regression only FEV_1 and increased diaphragmatic load, and not respiratory drive, predicted resting Pa,CO_2. Irrespective of CO_2 level, baseline central drive (represented by the mouth occlusion and pleural pressures) and CO_2 response are preserved in most patients with severe chronic obstructive pulmonary disease. Effective ventilation is inadequate in the more severely obstructed patients and this results in hypercapnia. Neuroventilatory coupling failure is an attractive explanation for chronic hypercapnia in these patients.

Use of Mouth Pressure Twitches Induced by Cervical Magnetic Stimulation To Assess Voluntary Activation of the Diaphragm—de Bruin PF, Watson RA, Khalil N, Pride NB. Eur Respir J 1998;12(3):672.

There is a need for a simple method to assess the adequacy of diaphragm activation during voluntary inspiratory efforts in patients with suspected respiratory muscle weakness. We have compared mouth (Pmo,t), oesophageal (Poes,t) and transdiaphragmatic (Pdi,t) twitch pressure elicited by cervical magnetic stimulation (CMS) in five normal men (mean (SD) age 32.2 (1.8) yrs) on two separate study days. Single magnetic stimuli were delivered at functional residual capacity during relaxation and during graded voluntary inspiratory efforts against a closed airway. As voluntary-effort transdiaphragmatic and oesophageal pressure increased, Pdi,t and Poes,t decreased linearly (r range, respectively, 0.82-0.98 and 0.87-0.95). During relaxation, Pmo,t was unreliable due to the poor transmission of intrathoracic pressure, but during inspiratory efforts, the relation between voluntary mouth pressure and Pmo,t was also linear (r range 0.84-0.95). On average, our subjects voluntarily generated 99, 100 and 102% of the maximum transdiaphragmatic, oesophageal and mouth pressures predicted by the respective linear regression equations. Pmo,t was correlated to both Poes,t and Pdi,t during inspiratory efforts, but not during relaxation. These studies confirm that twitch pressures induced by CMS during inspiratory efforts can be assessed at the mouth in normal subjects, providing a simple and non-invasive technique for assessing diaphragm activation during voluntary inspiratory efforts. Potentially, this technique could be made more sensitive and accurate and applied to detect submaximal efforts in patients.

Pulmonary Haemodynamics in Obstructive Sleep Apnoea: Time Course and Associated Factors—Schafer H, Hasper E, Ewig S, Koehler U, Latzelsberger J, Tasci S, Luderitz B. Eur Respir J 1998;12(3):679.

Changes in pulmonary artery pressure within an obstructive apnoea and elevations of transmural pulmonary artery pressure (Ppa,tm) towards the end of apnoea are well known. The purpose of our study was to examine which factors contribute to the increase of Ppa,tm in an apnoea. In addition, the time course of Ppa,tm and associated factors during a sleep study was investigated. We analysed the association of changes in arterial oxygen saturation (Sa,O_2), oesophageal pressure (Poes) to estimate intrathoracic pressure, systolic blood pressure (BPsys) to estimate left ventricular afterload, apnoea duration and the change in Ppa,tm (ΔPpa,tm) during the course of obstructive apnoeas. Consecutive apnoeas in nonrapid eye movement (NREM)-sleep at the beginning, the middle and the end of the sleep study were analysed in six patients with obstructive sleep apnoea. The mean systolic Ppa,tm was 28.0±12.1 mm Hg at the beginning of apnoea and 38.6±15.5 mm Hg at the end (ΔPpa,tm 10.5±7.4 mm Hg; $p<0.0001$). $\Delta Sa,O_2$ ($p<0.0001$; odds ratio (OR) 1.45; confidence interval (CI) 1.20-1.76) and ΔPoes ($p<0.001$; OR 1.22; CI 1.11-1.34) were independently associated with ΔPpa,tm in a multiple regression analysis. Apnoea duration as well as ΔPoes, ΔPpa,tm and $\Delta Sa,O_2$ were all significantly higher ($p<0.05$) in apnoeas at the middle of the

sleep study than at the beginning or the end. In conclusion, hypoxaemia and mechanical factors as an increase in negative thoracic pressure contribute to elevations of the transmural pulmonary artery pressure during an obstructive apnoea. The time course of pulmonary haemodynamics within a steep study reveals that the highest transmural pulmonary artery pressure occurs in the middle of the night with no progressive increase towards the end of the sleep study.

Maximum Rate of Change in Oesophageal Pressure Assessed from Unoccluded Breaths: An Option Where Mouth Occlusion Pressure Is Impractical—Hamnegard CH, Polkey MI, Kyroussis D, Mills GH, Green M, Bake B, Moxham J. Eur Respir J 1998;12(3):693.

The mouth occlusion pressure 100 ms after onset of inspiration (P0.1) is considered a clinically useful measure of the combined output of the respiratory centre and muscle pump. However, theoretical and practical difficulties can arise when using P0.1 in the assessment of patients with severe chronic obstructive pulmonary disease (COPD). It was hypothesized that the maximum rate of change in oesophageal pressure (dPoes,max/dt) may be an alternative to P0.1. To test this hypothesis P0.1 was compared with mean dPoes,max/dt measured from neighbouring unoccluded breaths in five normal subjects during CO_2 rebreathing. In all subjects a close correlation was found between both dPoes,max/dt and P0.1 and carbon dioxide tension (PCO_2). In six patients with severe COPD performing exhaustive treadmill walks, dPoes,max/dt was found to increase progressively with walking time. Mean dPoes,max/dt at the start was 6.2 cm H_2O x 100 ms^{-1} and at the finish was 18.7 cm H_2O x 100 ms($p<0.03$). In conclusion, the maximum rate of change in oesophageal pressure measured from unoccluded breaths could be an alternative in circumstances where it is not feasible to use measurements of the mouth occlusion pressure 100 ms after onset of inspiration.

Surfactant Composition Reflects Lung Overinflation and Arterial Oxygenation in Patients with Acute Lung Injury—Bersten AD, Doyle IR, Davidson KG, Barr HA, Nicholas TE, Kermeen F. Eur Respir J 1998;12(2):301.

Pulmonary surfactant abnormalities have consistently been documented in patients with acute lung injury (ALI), however, there is little evidence directly correlating them to altered respiratory mechanics. To explore this further, surfactant composition was measured in lung aspirate fluid collected on 15 occasions from 10 patients with ALI. The composition was compared with lung aspirate fluid from 11 intubated patients prior to elective cardiac surgery (CS), and bronchoalveolar lavage fluid from 16 normal subjects. In both the ALI and cardiac groups the proportion of disaturated phospholipids (DSP) and phosphatidylcholine was reduced. Plasma levels of surfactant proteins-A and -B (SP-A and -B) were elevated, but were unrelated to alveolar surfactant levels. In the ALI group, and the ALI + CS group, DSP, normalized to the total phospholipid content, sphingomyelin (SPH), and urea, showed strong direct correlations with arterial oxygen tension/inspiratory oxygen fraction (all $p \leq 0.01$). In the ALI group, normalized DSP was also directly related to the elastance of the positive end-expiratory pressure-induced increase in the end-expiratory lung volume (all $p \leq 0.02$), and indirect correlations were found with a measure of lung overinflation (%E2; all $p \leq 0.01$). We conclude that surfactant composition correlates with lung function abnormalities in acute lung injury and cardiac patients, and that both groups had elevated plasma surfactant proteins-A and -B levels, consistent with a concurrent increase in alveolocapillary permeability.

Standardization of Ambulatory Peak Flow Monitoring: The Importance of Recent β2-Agonist Inhalation—Reddel HK, Ware SI, Salome CM, Marks GB, Jenkins CR, Woolcock AJ. Eur Respir J 1998;12(2):309.

Standardization of conditions for peak expiratory flow (PEF) monitoring is much more difficult in practice than for laboratory spirometry. Patients are usually asked to record PEF before medication. The aim of this study was to determine the effect of prior bronchodilator use on PEF outcome measures in a clinical trial. Electronic PEF records from 43 subjects with poorly controlled asthma were examined to determine the frequency with which β2-agonist was inhaled <4 h before PEF measurement, as such PEF are potentially 'postbronchodilator'. The effect of inclusion of such PEF values on improvement in PEF outcome measures after 8 weeks of inhaled budesonide was calculated. Subjects were asked to record PEF before medication. During run-in, the median frequency of postbronchodilator PEF was 29%, falling to 0% after 8 weeks of budesonide. Inclusion of postbronchodilator PEF led to an overestimation of average morning, evening and daily PEF during run-in ($p < 0.001$). Improvement in these indices with treatment was, therefore, underestimated. Minimum morning PEF expressed as per cent personal best was unaffected. Subjects may not be able to withhold β2-agonist for 4 h before every peak flow reading. This may change as the level of asthma control changes, leading to a systematic bias in clinical trial endpoints or inaccuracy in individual treatment decisions. Simple changes to peak expiratory flow instructions and analysis are proposed.

Worldwide Variations in the Prevalence of Asthma Symptoms: The International Study of Asthma and Allergies in Childhood Eur Respir J 1998;12(2):315.

The International Study of Asthma and Allergies in Childhood (ISAAC) was designed to allow comparisons between populations in different countries. ISAAC Phase One, reported here, used standardized simple surveys which were conducted among representative samples of school children from centres in most regions of the world. Two age groups (13-14 and 6-7 yrs) with approximately 3,000 children in each group were studied in each centre. The 13-14 yr olds (n=463,801) were studied in 155 centres (56 countries) and the 6-7 yr olds (n=257,800) were studied in 91 centres (38 countries). There were marked variations in the prevalence of asthma symptoms with up to 15-fold differences between countries. The prevalence of wheeze in the last 12 months ranged from 2.1-32.2% in the older age group and 4.1-32.1% in the younger age group and was particularly high in English speaking countries and Latin America. A video questionnaire completed in the older age group in 99 centres (42 countries) showed a similar pattern. The major differences between populations found in the International Study of Asthma and Allergies in Childhood Phase One are likely to be due to environmental factors. The results provide a framework for studies between populations in contrasting environments which are likely to yield new clues about the aetiology of asthma.

Nebulized Magnesium Sulphate versus Nebulized Salbutamol in Acute Bronchial Asthma: A Clinical Trial—Mangat HS, D'Souza GA, Jacob MS. Eur Respir J 1998;12(2):341.

Intravenous magnesium sulphate ($MgSO_4$) has successfully been used in the treatment of acute asthma. The present study investigated the efficacy of nebulized $MgSO_4$ as a bronchodilator in acute asthma as compared to nebulized salbutamol. This was a randomized, double-blind, controlled clinical trial. Asthmatics aged 12-60 yrs in acute exacerbation, with a peak expiratory flow (PEF) <300 L x min^{-1}, not having taken bronchodilators and not requiring assisted ventilation were included. Patients were randomized to receive treatment with serial nebulizations of either 3 mL (3.2% solution, 95 mg) $MgSO_4$ solution or 3 mL (2.5 mg) salbutamol solution. All patients were also given 100 mg hydrocortisone i.v., and were monitored continuously for 2 h after which they were given supplemental treatment (if and when needed) and either discharged or admitted. Fischl index, PEF improvements (in % predicted) and admission rates were the outcome variables. Thirty-three patients were studied. Fischl score improvement was comparable and significant in both groups (4.31 to 0.43 in the $MgSO_4$ group and 4.29 to 0.76 in the salbutamol group). The increase in PEF was statistically significant and

comparable in both groups (by 35% pred in the $MgSO_4$ and by 42% pred in the salbutamol group). Two patients warranted admission in the salbutamol group and one in the $MgSO_4$ group. Nebulized $MgSO_4$ had a significant bronchodilatory effect in acute asthma. This effect was not significantly different from that of nebulized salbutamol.

Effects of High-Altitude Periodic Breathing on Sleep and Arterial Oxyhaemoglobin Saturation—Salvaggio A, Insalaco G, Marrone O, Romano S, Braghiroli A, Lanfranchi P, et al. Eur Respir J 1998;12(2):408.

This study aimed to investigate the effect of periodic breathing (PB) at high altitude on sleep structure and arterial oxygen saturation (Sa_1O_2). Five healthy subjects underwent polysomnographic studies at sea level, and during the first and the fourth week of sojourn at 5,050 m. Their breathing pattern, sleep architecture and Sa_1O_2 were analysed. PB was detected in the high-altitude studies during nonrapid eye movement (NREM) sleep and tended to increase from the first to the fourth week. Stages 3-4 were absent in four subjects at the first week, but only in one at the fourth week, irrespective of the amount of PB. The arousal index was 11.6 ± 3.8 at sea level, 30.1 ± 15.5 at the first week at altitude and 33.0 ± 18.2 at the fourth week. At altitude, arousal index in NREM sleep was higher during PB than during regular breathing. In NREM sleep, the mean highest Sa_1O_2 levels in NREM epochs with PB were higher than in those with regular breathing by 2.8 ± 1.7% at the first week and 2.9 ± 1.5% at the fourth week ($p < 0.025$). From the first to the fourth week, mean Sa_1O_2 increased significantly during wakefulness (5.6%), NREM (5.2% with regular breathing and 5.3% with PB) and rapid eye movement sleep (7.6%). The data demonstrate a slight role of periodic breathing in altering sleep architecture at high altitude and also show that periodic breathing induces only a minor improvement in arterial oxygen saturation during nonrapid eye movement sleep.

Pharmacologic Treatment of Sleep-Disordered Breathing—Rudgel DW, Thanakitcharu S. Am J Respir Crit Care Med 1998;158(3): 691.

Available literature on the use of pharmacologic agents for the treatment of sleep-disordered breathing was reviewed by evidenced-based methodology. Evidence tables were created and studies were graded according to study design and the number of subjects included. Scores for each group of studies evaluating each pharmacologic agent were established so that the quality of research for different drugs could be compared. The use of various ventilatory stimulants, psychotropic drugs, and antihypertensive agents were reviewed. The most objective data are available on theophylline and opioid antagonist/nicotine groups. Although more controlled studies would be helpful, relatively clear-cut indications for the use of ventilatory stimulants exist for hypercapnic obesity-hypoventilation patients (medroxyprogesterone), myxedema (thyroid replacement), central apnea (acetazolamide), and periodic breathing in congestive heart failure (theophylline). Few randomized, well-controlled trials have been published that evaluate pharmacologic agents in the treatment of classic OSA. To date, no one agent stands out as being useful for OSA. Future research will need to characterize subjects so that various subsets of patients can be tried on one or on a combination of various pharmacologic agents.

Concepts of Fever—Mackowiak PA. Arch Intern Med 1998;158(17):1870.

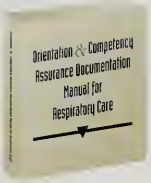
If asked to define fever, most physicians would offer a thermal definition, such as 'fever is a temperature greater than. . . .' In offering their definition, many would ignore the importance of the anatomic site at which temperature measurements are taken, as well as the diurnal oscillations that characterize body temperature. If queried about the history of clinical thermometry, few physicians could identify the source or explain the pertinacity of the belief that 98.6 degrees F (37.0 degrees C) has special meaning vis-a-vis normal body temperature. Fewer still could cite the origin of the thermometer or trace the evolution of modern concepts of clinical thermometry. Although many would have some knowledge of the fundamentals of thermoregulation and the role played by exogenous and endogenous pyrogens in the induction of fever, few would have more than a superficial knowledge of the broad biological activities of pyrogenic cytokines or know of the existence of an equally complex and important system of endogenous cryogens. A distinct minority would appreciate the obvious paradoxes inherent in an enlarging body of data concerned with the question of fever's adaptive value. The present review considers many of these issues in the light of current data.

Randomized Controlled Trial of Pulmonary Rehabilitation in Severe Chronic Obstructive Pulmonary Disease Patients, Stratified with the MRC Dyspnoea Scale—Wedzicha JA, Bestall JC, Garrod R, Garnham R, Paul EA, Jones PW. Eur Respir J 1998;12(2):363.

This study tested the hypothesis that severity of respiratory disability may affect the outcome of pulmonary rehabilitation. In this randomized, controlled study, 126 patients with chronic obstructive pulmonary disease (COPD) were stratified for dyspnoea using the Medical Research Council (MRC) dyspnoea score into MRC3/4 (Moderate) (n=66) and MRC 5 (Severe) dyspnoeic (n=60) groups. The patients were randomly assigned to an eight week programme of either exercise plus education (Exercise group) or education (Control group). Education and exercise programmes for the moderately dyspnoeic patients were carried out in a hospital outpatient setting. Severely dyspnoeic patients were all treated at home. Those in the Exercise group received an individualized training programme. There was a significant improvement in shuttle walking distance in the moderate dyspnoeic group, who received exercise training; baseline (mean ± SEM) 191 ± 22 m, post-rehabilitation 279 ± 22 m ($p<0.001$). There was no improvement in exercise performance in the severely dyspnoeic patients receiving exercise. Neither group of control patients improved. Health status, assessed by the Total Chronic Respiratory Disease Questionnaire score, increased in the moderately dyspnoeic patients receiving exercise from 80 ± 18 to 95 ± 17 ($p<0.0001$) after rehabilitation. Much smaller changes were seen in the other three groups. Improvement in exercise performance and health status in patients with chronic obstructive pulmonary disease after an exercise programme depends on the initial degree of dyspnoea.

Emotional Status Does Not Alter Exercise Tolerance in Patients with Chronic Obstructive Pulmonary Disease—Borak J, Chodosowska E, Matuszewski A, Zielinski J. Eur Respir J 1998;12(2):370.

Exercise tolerance in chronic obstructive pulmonary disease (COPD) patients has been shown to be related to airway limitation and dyspnoea, but little is known about the effects of an emotional status on physical performance. We examined 49 COPD patients with a wide spectrum of airway limitation severity and hypoxaemia. Exercise tolerance was evaluated using the Six-minute Walking Distance Test (6MWD), dyspnoea at rest and on exercise was measured using the visual analogue scale, and the emotional status was evaluated using the battery of psychological tests. The average 6MWD (mean ± SD) was 355 ± 112 m. In the majority of patients a fall in arterial blood oxygen saturation (Sa_1O_2) on exercise of >3% was found. The mean dyspnoea score of 21 ± 19 at rest increased to 66 ± 19 on exercise. All subjects demonstrated an increased level of anxiety. The majority also demonstrated elevated emotional tension, and half of the study group showed signs of depression. Step-wise multiple regression analysis with results of 6MWD as dependent and other studied variables as independent variables showed that exercise tolerance depended mainly on airway limitation. The forced expiratory volume in one second (FEV_1) explained 24% of the variance. The forced vital capacity added a further 10%, and arterial blood carbon dioxide tension contributed 7%. The dys-



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pnoea level on exercise added only 0.9%. All four variables explained 42% of the variance. There was no correlation between 6MWD and any of the variables characterizing the emotional status. We conclude that the emotional status of chronic obstructive pulmonary disease patients is characterized by an increased level of psychological tension, anxiety and depression, but these do not affect exercise tolerance as assessed by the six-minute walking distance test.

The Haemodynamic Response to Exercise in Chronic Obstructive Pulmonary Disease: Assessment by Impedance Cardiography—Bogaard HJ, Dekker BM, Arntzen BW, Woltjer HH, van Keimpema AR, Postmus PE, de Vries PM. Eur Respir J 1998;12(2):374.

This study aimed to determine the differences in haemodynamic responses to a standard incremental exercise test between outpatients with chronic obstructive pulmonary disease (COPD) and age-matched controls and to discover the relationship between severity of airflow obstruction and exercise haemodynamics in COPD. Twenty-two male patients with COPD (forced expiratory volume in one second (FEV_1)/vital capacity (VC)) <80% predicted) and 20 age-matched male controls performed an incremental exercise test (10 W x min^{-1}) with ventilatory function and changes in stroke volume (ΔSV) and cardiac output (ΔCO) measured by means of electrical impedance cardiography (EIC). Submaximal ΔSV and ΔCO were lower in COPD patients. Peak exercise ΔSV were equal in patients and controls (128 ± 33 versus 129 ± 29%, p=0.98), whereas peak ΔCO was lower in patients (COPD versus controls: 232 ± 71 versus 289 ± 54%, p<0.005). In COPD patients, FEV_1 (% pred) was significantly correlated to ΔSV at all submaximal exercise intensities, to peak exercise ΔSV and to peak exercise ΔCO. FEV_1/VC (% pred) was significantly correlated to ΔSV at 30 and 60 W. In conclusion, in chronic obstructive pulmonary disease an aberrant haemodynamic response to exercise was found, especially in patients with severe airflow obstruction. This aberrant response is related to the degree of airflow obstruction and may limit exercise performance in patients with severe chronic obstructive pulmonary disease.

Cigarette Smoke Inhalation and Lung Damage in Smoking Volunteers—Clark KD, Wardrobe-Wong N, Elliott JJ, Gill PT, Tait NP, Snashall PD. Eur Respir J 1998;12(2):395.

Cigarette smoking is the dominant risk factor for chronic obstructive pulmonary disease (COPD) but only 10-15% of smokers develop the condition. Risk does not relate closely to cumulative cigarette consumption, perhaps because smokers vary in the degree and depth of smoke inhalation. This study examined the role of smoke inhalation in the development of COPD. Eighty current smokers and 20 lifetime nonsmoking volunteers (aged 35-65 yrs) were recruited. Lung function variables were measured and high-resolution computed tomography (HRCT) scans performed. Smoke inhalation was assessed by CO boost (the increment of expired carbon monoxide 5 min after smoking a cigarette) and serum cotinine. Mean CO boost was 6.3 parts per million (ppm) in smokers with low CO transfer coefficients (KCO) and 2.9 ppm in those with normal KCO (p=0.006); 7.2 ppm in smokers with both HRCT-defined emphysema and a low KCO and 2.6 ppm in those with neither abnormality (p=0.002); 4.5 ppm in smokers with HRCT-defined emphysema alone and 2.8 ppm in those without (p=0.08). Mean serum cotinine was 328 ng x mL^{-1} in smokers with chronic productive cough and 243 ng x mL^{-1} in those without (p=0.005). Lifetime nonsmokers had normal HRCT scans, lung function and serum cotinine. Emphysema is associated with high alveolar smoke exposure as measured by CO boost. Productive coughing is associated with high nicotine uptake, probably from airway smoke particle deposition.

Treatment Of Cheyne-Stokes Respiration with Nasal Oxygen and Carbon Dioxide—Andreas S, Weidel K, Hagenah G, Heindl S. Eur Respir J 1998;12(2):414.

Cheyne-Stokes respiration (CSR) is common in patients with congestive heart failure (CHF) and is associated with significant nocturnal O_2 desaturation, arousals and sympathetic activation. Nocturnal O_2 reduces CSR by only about 50%. More complete suppression of CSR may be achieved by adding CO_2 to O_2. This study therefore aimed to evaluate the effects of nocturnal O_2 plus CO_2 on CSR, sleep and sympathetic activation. Nine patients with CHF (age 59 ± 5 yrs; left ventricular ejection fraction 17.8 ± 1.2% (mean ± SEM) were studied in a cross-over, single-blind, placebo-controlled trial. After an accommodation night the patients were randomly assigned to one night each of O_2 plus CO_2 as well as air applied by nasal prongs. Nocturnal O_2 plus CO_2 reduced the duration of CSR as percentage of total sleep time (48.0 ± 10 versus 7.4 ± 2.0%; p=0.008) and increased arterial oxygen saturation (Sa_1O_2) as well as mean transcutaneous carbon dioxide tension (Ptc_1CO_2) (5.2 ± 0.3 kPa (39 ± 2 mm Hg) versus 5.7 ± 0.3 kPa (43 ± 2 mm Hg) p=0.011). Sleep did not improve and arousals were not reduced. Plasma noradrenaline was higher on the treatment night (486 ± 116 versus 669 ± 163 ng x L^{-1}; p=0.035). In conclusion, nocturnal O_2 plus CO_2 improves Cheyne-Stokes respiration in patients with congestive heart failure but has adverse effects on the sequel of Cheyne-Stokes respiration, namely sympathetic activation.

Effect of Oxygen on Breathing Irregularities during Haemodialysis in Patients with Chronic Uraemia—Yap JC, Wang YT, Poh SC. Eur Respir J 1998;12(2):420.

Hypoxaemia and breathing irregularities have been shown to occur during haemodialysis in patients with chronic renal failure. This study examined the role of hypoxia in the genesis of the irregular breathing during haemodialysis. The ventilatory patterns using respiratory inductance plethysmography and arterial blood gases were studied in seven males with chronic renal failure on long-term haemodialysis. The study was carried out before and during dialysis on one day without (D1) and another day with intranasal oxygen at 4 L x min^{-1} (D2). On D1, mean (SD) arterial oxygen tension (Pa_1O_2) fell 1.9 (0.9) kPa (p<0.001) and mean minute ventilation (yE) fell 1.9 (1.1) L x min^{-1} (p<0.01) during dialysis. The arterial carbon dioxide tension (Pa_1CO_2) did not show a significant decrease (4.7 (0.2) kPa before and 4.6 (0.2) kPa during dialysis). Cumulative number of apnoeas was 64 and the coefficients of variation (COV) of respiratory frequency (fR) and tidal volume (V_T) were 29.6 (11.9) and 38.2 (11.9)%, respectively. On D2, mean Pa_1O_2 remained stable (20.4 (4.1) kPa before, 21.3 (4.1) kPa during dialysis). There was no significant change in mean yE (6.4 (0.9) L x min^{-1} before, 5.5 (0.5) L x min^{-1} during dialysis). Pa_1CO_2 decrease was not significant but the fall was greater (4.8 (0.1) kPa before, 45 (0.5) kPa during dialysis). Cumulative number of apnoeas was 94 and the COVs of fR and V_T were 35.8 (5.1) and 40.5 (11.3)%, respectively. Oxygen administration did not significantly affect the haemodialysis-induced changes in ventilation and breathing pattern, despite a significant protective effect from the fall in arterial oxygen tension. It was concluded that the fall in arterial oxygen tension is not the main determinant of breathing irregularities during haemodialysis.

Cough and Sleep in Inner-City Children—Fuller P, Picciotto A, Davies M, McKenzie SA. Eur Respir J 1998;12(2):426.

This study aimed to determine whether cough at night keeps children awake, to describe the relationship between children's cough and sleep and to report parents' perceptions of their children's cough and sleep. Thirty-nine children with reported persistent cough at night (>3 weeks) were recruited and studied for 6 nights by video-recording. Coughs were counted and sleep state was coded for awake, restless sleep and quiet sleep. The relationships between cough and sleep state between subjects and within subjects were examined by correlation and regression. After night 2 the parents were asked whether their child had coughed or had disturbed sleep and after night 6 they were asked whether there had been any change. There was

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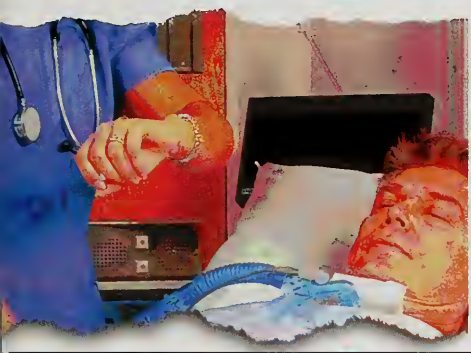

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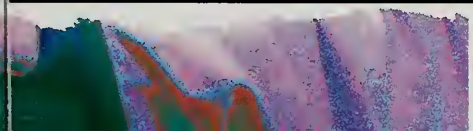
Patient to ICU 4 Change Ventilator



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a weak relationship between log percentage of the night awake and log number of coughs ($r = 0.13$, SE 0.036), and log (percentage of the night awake plus restless sleep) and log number of coughs ($r = 0.016$, SE 0.0071). If the relationship between cough and sleep state is causal, halving the number of coughs will reduce the percentage of the night awake by 9% (95% confidence interval (CI) 4-15%) and percentage awake and restless by 1% (95% CI 0-2%). All but one parent correctly identified coughing and 82% detected change. Most could not comment on their child's sleep. Improvement in cough would result in little reduction in either the percentage of the night awake or awake and restless in the average child in the population studied. Parents could detect whether their children were coughing but not whether their sleep was disturbed.

Assessment of Accuracy and Applicability of a New Electronic Peak Flow Meter and Asthma Monitor—Richter K, Kanniess F, Mark B, Jorres RA, Magnussen H. Eur Respir J 1998;12(2):457.

The aim of this study was to assess the accuracy and applicability of a portable electronic peak flow meter combined with an asthma monitor (AM1, Jaeger, Germany) which measures peak expiratory flow (PEF), forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). The technical accuracy in PEF, FEV_1 and FVC measurement was tested according to American Thoracic Society (ATS) criteria for monitoring devices using a flow generator. In addition, the effect of connecting a heated screen pneumotachograph (PT) to the AM1 was determined and the accuracy in FEV_1 determinations was evaluated by simultaneous measurements in 49 normal volunteers. The devices tested fulfilled all ATS criteria for monitoring devices with respect to the accuracy of PEF, FEV_1, and FVC measurements. The conditions of intra- and interdevice variability were satisfied in all cases. Compared with the PT, the AM1 showed about 4% lower values in FEV_1, as measured in the 49 subjects. In conclusion, the electronic peak flow meter and asthma monitor AM1 yielded valid measurements of peak expiratory flow and forced expiratory volume in one second, which matched the accuracy criteria of the American Thoracic Society standards for monitoring devices.

Drug Output from Nebulizers is Dependent on the Method of Measurement—Barry PW, O'Callaghan C. Eur Respir J 1998;12(2):463.

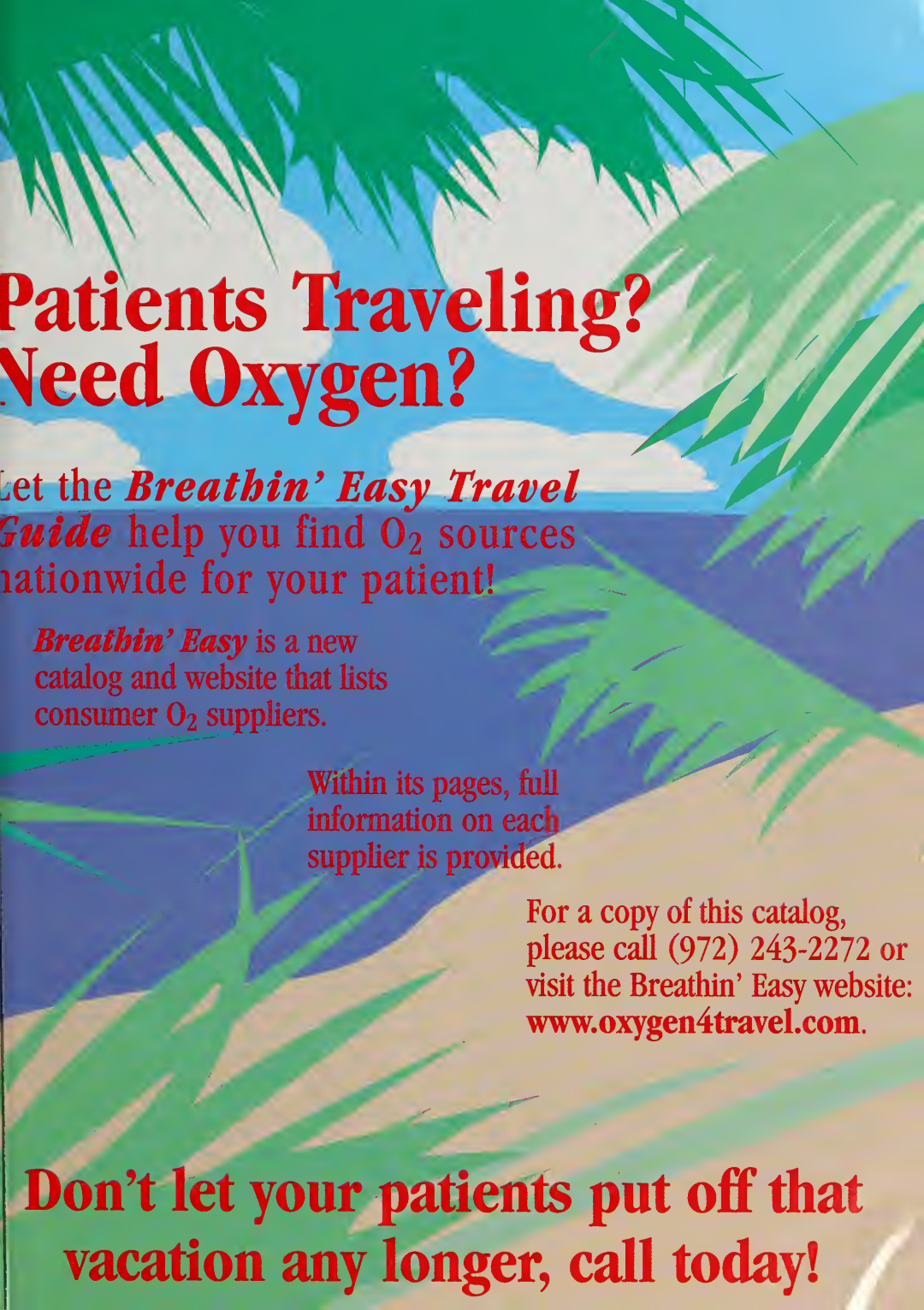
The objective of this study was to determine whether current regulatory methods for assessing the output of nebulizers are appropriate for the delivery of nebulized steroid suspensions to patients. We studied a conventional jet nebulizer (the Intersurgical Cirrus), an open-vent nebulizer (the Medicaid Sidestream) and a breath-enhanced nebulizer (the Pari LC Plus), using a constant sampling flow or a sinusoidal pump to represent the breathing pattern of children from 6 months to adulthood. Recovery of budesonide released from the nebulizers onto filters was reduced when using breathing simulation compared with constant flow, and this reduction was greatest for the conventional nebulizer (Cirrus, 103 microg with constant flow to 4.4 microg with a 50 mL tidal volume; Pari, 176 microg to 25 microg). The open-vent nebulizer deposited very little budesonide on the filter at lower tidal volumes (4.5 microg with a 50 mL tidal volume), possibly because the enhanced flow of aerosol laden air was greater than the inspiratory flow from the breathing simulator. The output of the LC plus was reduced at high flow, from 176 microg at 20 L x min^{-1} to 93 microg at 60 L x min^{-1}. Overall, the measured output varied by up to 700%, depending on the method used. These results suggest that breathing patterns dramatically alter the measured output of different nebulizers and that breathing simulation should be included as part of their assessment.

A New Method for Measuring Aerosol Nebulizer Output Using Radioactive Tracers—Gatnash AA, Chandler ST, Connolly CK. Eur Respir J 1998;12(2):467.

Reproducibility and comparability of bronchial challenge tests depends critically on accurate assessment of nebulizer output. Evaporation during nebulization means that simple weighing is inaccurate, overestimating the delivered dose of active ingredient. We wanted to quantify this effect in the context of intermittent nebulization, using a dosimeter as used in bronchial provocation tests. Output of three types of nebulizer, from the MEFAR dosimeter, was measured by radioactive tracer, using a standard solution of technetium-99m-pertechnetate (1.5 kBq x mL^{-1}) in 4 mL of normal saline. The aerosol was impacted by suction onto a microfilter, and the radioactivity measured. Nebulizers were weighed before and after nebulization. Ratio of nebulized volume calculated from the radioactivity on the filter, to the total volume loss by weight, was expressed as nebulized ratio. The effect on output of two concentrations of methacholine, two tracers of different weights, and change in temperature, were assessed. Nebulized ratio varied between 44.1-71.6%. Results were more consistent within the same type of nebulizer than between different makes. Neither changes in molar concentration nor molecular weight affected nebulizer output or nebulized ratio. Mean nebulized ratio was 58.5%, showing that calibration by weighing, overestimates the delivered dose by a factor of approximately two. Measuring radioactivity eluted from a microfilter, onto which nebulized output had been impacted proved to be a satisfactory method of calibration.

Exogenous Surfactant Preserves Lung Function and Reduces Alveolar Evans Blue Dye Influx in a Rat Model of Ventilation-Induced Lung Injury—Verbrugge SJ, Vazquez de Anda G, Gommers D, Neggers SJ, Sorm V, Bohm SH, Lachmann B. Anesthesiology 1998;89(2):467.

BACKGROUND: Changes in pulmonary edema infiltration and surfactant after intermittent positive pressure ventilation with high peak inspiratory lung volumes have been well described. To further elucidate the role of surfactant changes, the authors tested the effect of different doses of exogenous surfactant preceding high peak inspiratory lung volumes on lung function and lung permeability. METHODS: Five groups of Sprague-Dawley rats (n = 6 per group) were subjected to 20 min of high peak inspiratory lung volumes. Before high peak inspiratory lung volumes, four of these groups received intratracheal administration of saline or 50, 100, or 200 mg/kg body weight surfactant; one group received no intratracheal administration. Gas exchange was measured during mechanical ventilation. A sixth group served as nontreated, nonventilated controls. After death, all lungs were excised, and static pressure-volume curves and total lung volume at a transpulmonary pressure of 5 cm H_2O were recorded. The Gruenwald index and the steepest part of the compliance curve (Cmax) were calculated. A bronchoalveolar lavage was performed; surfactant small and large aggregate total phosphorus and minimal surface tension were measured. In a second experiment in five groups of rats (n = 6 per group), lung permeability for Evans blue dye was measured. Before 20 min of high peak inspiratory lung volumes, three groups received intratracheal administration of 100, 200, or 400 mg/kg body weight surfactant; one group received no intratracheal administration. A fifth group served as nontreated, nonventilated controls. RESULTS: Exogenous surfactant at a dose of 200 mg/kg preserved total lung volume at a pressure of 5 cm H_2O, maximum compliance, the Gruenwald index, and oxygenation after 20 min of mechanical ventilation. The most active surfactant was recovered in the group that received 200 mg/kg surfactant, and this dose reduced minimal surface tension of bronchoalveolar lavage to control values. Alveolar influx of Evans blue dye was reduced in the groups that received 200 and 400 mg/kg exogenous surfactant. CONCLUSIONS: Exogenous surfactant preceding high peak inspiratory lung volumes prevents impairment of oxygenation, lung mechanics, and minimal surface tension of bronchoalveolar lavage fluid and reduces alveolar influx of Evans blue dye. These data indicate that surfactant has a beneficial effect on ventilation-induced lung injury.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Trends in Infectious Disease Hospitalizations in the United States, 1980-1994 —Simonsen L, Conn LA, Pinner RW, Teutsch S. Arch Intern Med 1998;158(17):1923.

BACKGROUND: A recent study concluded that between 1980 and 1992, deaths from infectious diseases increased 58%. This article explores trends in infectious diseases as a cause of hospitalization. METHODS: We analyzed data from the National Hospitalization Discharge Survey for 1980 through 1994 using a previously developed approach to evaluate infectious diseases in data coded according to the International Classification of Diseases, Ninth Revision. RESULTS: Between 1980 and 1994, the rate of hospitalizations in the United States declined approximately 33%; hospitalizations occurred at a rate of 133 ± 5 per 1000 US population (35 million ± 1 million discharges) in 1994. The rate of hospitalization for infectious diseases declined less steeply—12% during this interval—resulting in an increased proportion of hospitalizations because of infectious diseases. In 1994, the rate of hospitalizations for infectious diseases was 15.4 ± 0.7 per 1000 US population (4.0 million ± 0.2 million discharges). The fatality rate associated with hospitalizations for infectious diseases increased from 1.9% ± 0.1% to 4.0% ± 0.3%, attributable to increased hospitalizations of elderly persons and an increased fatality rate among those younger than 65 years. Among selected categories, hospitalizations for human immunodeficiency virus infections and acquired immunodeficiency syndrome, prosthetic device infections, sepsis, and mycosis increased substantially, and hospitalizations for upper respiratory tract infections, pelvic inflammatory disease, and oral infections declined sharply. Hospitalizations for lower respiratory tract infections constituted 37% of all infectious disease hospitalizations in 1994. CONCLUSIONS: Considering hospitalizations as a dimension of the burden of infectious diseases involves an array of factors: secular trends in hospitalization, changing case management practices, demographic changes, and trends in the variety of infectious diseases themselves. Increases in the proportions of hospitalizations because of infectious diseases during years when hospitalizations for all causes were decreasing reflect an increasing burden of infectious diseases in the United States between 1989 and the mid-1990s.

In Vitro Performance of Three Combinations of Spacers and Pressurized Metered Dose Inhalers for Treatment in Children Berg E, Madsen J, Bisgaard H. Eur Respir J 1998;12(2):472.

The performance of pressurized metered dose inhalers (pMDIs) and spacers in correct dose recommendations is important, but limited information on dose delivery and fine-particle dose from different combinations of spacers and pMDIs is available. In this study, three combinations of spacers and pMDIs were investigated: NebuChamber and AeroChamber with budesonide pMDI and Babyhaler with fluticasone propionate pMDI. Doses were withdrawn onto a filter either with a breathing simulator (dose to ventilator) or with constant flow (maximal dose). The fine-particle dose was assessed with a cascade impactor (Andersen Sampler). The effect of repeated use and cleaning of the spacers on the passive fallout of aerosol within the spacers was determined by evacuating the dose on a filter 2, 5, 10 and 30 s after actuating the spray. The drugs were quantified by liquid chromatography. The NebuChamber delivered the highest doses, both maximal dose and dose to ventilator. The recovered doses (means±SD) were 55±6% and 51±2%, respectively, of the delivered dose from the pMDI. The corresponding results for the Babyhaler were 41±7% and 24±4% and for the Aerochamber 27±3% and 17±3%. The passive fallout of aerosol, determined as half-life (t1/2) was around approximately 30 s for the NebuChamber, 9-15 s for the Babyhaler and approximately 10 s for the AeroChamber. The present study confirms that there are significant differences in dose output from different combinations of pressurized metered dose inhalers and spacers, with the NebuChamber giving the highest dose, both as delivered dose and in droplets <4.7 microm. Interactions with the spacer material, dead space in the inspiratory line and entrainment of air during inhalation due to inefficient valve control could account for these differences.

Qualitative Aspects of Exertional Dyspnea in Patients with Interstitial Lung Disease—O'Donnell DE, Chau LKL, Webb KA. J Appl Physiol 1998;84(6):2000.

We compared qualitative and quantitative aspects of perceived exertional dyspnea in patients with interstitial lung disease (ILD) and normal subjects and sought a physiological rationale for their differences. Twelve patients with ILD [forced vital capacity = 64 ± 4 (SE) % predicted] and 12 age-matched normal subjects performed symptom-limited incremental cycle exercise tests with measurements of dyspnea intensity (Borg scale), ventilation, breathing pattern, operational lung volumes, and esophageal pressures (P_{es}). Qualitative descriptors of dyspnea were selected at exercise cessation. Both groups described increased "work and/or effort" and "heaviness" of breathing; only patients with ILD described "unsatisfactory inspiratory effort" (75%), "increased inspiratory difficulty" (67%), and "rapid breathing" (58%) ($p < 0.05$ patients with ILD vs normal subjects). Borg-O_2 uptake (V_{O_2}) and Borg-ventilation slopes were significantly greater during exercise in patients with ILD ($p < 0.01$). At peak exercise, when dyspnea intensity and inspiratory effort (P_{es}-to-maximal inspiratory pressure ratio) were similar, the distinct qualitative perceptions of dyspnea in patients with ILD were attributed to differences in dynamic ventilatory mechanics, ie, reduced inspiratory capacity, heightened P_{es}-to-tidal volume ratio, and tachypnea. Factors contributing to dyspnea intensity in both groups were also different: the best correlate of the Borg-V_{O_2} slope in patients with ILD was the resting tidal volume-to-inspiratory capacity ratio ($r = 0.58$, $p < 0.05$) and in normal subjects was the slope of P_{es}-to-maximal inspiratory pressure ratio over V_{O_2} ($r = 0.60$, $p < 0.05$).

Smaller Lungs in Women Affect Exercise Hyperpnea—McClaran SR, Harms CA, Pegelow DF, Dempsey JA. J Appl Physiol 1998; 84(6):1872.

We subjected 29 healthy young women (age: 27 ± 1 y) with a wide range of fitness levels [maximal oxygen uptake (VO_{2max}): 57 ± 6 mL · kg-1 · min-1; 35–70 mL · kg-1 · min-1] to a progressive treadmill running test. Our subjects had significantly smaller lung volumes and lower maximal expiratory flow rates, irrespective of fitness level, compared with predicted values for age- and height-matched men. The higher maximal workload in highly fit (VO_{2max} >57 mL · kg-1 · min-1, n = 14) vs less-fit (VO_{2max} < 56 mL · kg-1 · min-1, n = 15) women caused a higher maximal ventilation (V_E) with increased tidal volume (V_T) and breathing frequency (f) at comparable maximal VT/vital capacity (VC). More expiratory flow limitation (EFL; 22 ± 4% of V_T) was also observed during heavy exercise in highly fit vs less-fit women, causing higher end-expiratory and end-inspiratory lung volumes and greater usage of their maximum available ventilatory reserves. *He*O_2 (79% He-21% O_2) vs room air exercise trials were compared (with screens added to equalize external apparatus resistance). *He*O_2 increased maximal expiratory flow rates (20–38%) throughout the range of VC, which significantly reduced EFL during heavy exercise. When EFL was reduced with HeO_2, VT, and VE (+16 ± 2 L/min) were significantly increased during maximal exercise. However, in the absence of EFL (during room air exercise), HeO_2 had no effect on *VE*. We conclude that smaller lung volumes and maximal flow rates for women in general, and especially highly fit women, caused increased prevalence of EFL during heavy exercise, a relative hyperinflation, an increased reliance on fb, and a greater encroachment on the ventilatory "reserve." Consequently, *VT* and *VE* are mechanically constrained during maximal exercise in many fit women because the demand for high expiratory flow rates encroaches on the airways' maximum flow-volume envelope.

Pressure Support Ventilation, Patient-Ventilator Synchrony, and Ventilator Algorithms

Pressure support ventilation (PSV) has enjoyed relatively wide acceptance by the medical community, owing to a perceived improvement in patient comfort.[1,2] Simplicity has also been a hallmark of PSV. The clinician need only set the pressure limit, inspired oxygen concentration, and end-expiratory pressure level. Frequency, tidal volume, inspiratory-to-expiratory-time ratio, and flow are jointly controlled by the patient (effort and impedance) and the ventilator's PSV algorithm. The latter can often explain the changes in patient comfort observed when using different ventilators to provide PSV.

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In this issue, Yamada and Du report the results of a laboratory comparison of 3 ventilators in the pressure support mode.[3] Their results suggest that, under changing simulated patient demand and variable compliance and resistance, patient-ventilator synchrony can be adversely affected by the ventilator's algorithm. This finding is not unexpected, but requires some understanding of ventilator breath delivery characteristics to make sense.

Every breath has a trigger (switches the ventilator from expiration to inspiration), limit (constant variable that does not cause inspiration to end), and cycle (switches the ventilator from inspiration to expiration) variable. By definition, PSV is a patient-triggered, pressure-limited, flow-cycled mode of ventilatory support. Another variable in the PSV breath is the speed at which the ventilator reaches the pressure limit. In some ventilators this attack rate or rise time is pre-set, in others it is adjustable, and in others it can automatically adjust to increases or decreases in patient demand.[2] With respect to the work of breathing, the fastest trigger and the fastest attack rate provide the lowest measured work of breathing. This is particularly true in a lung model. In patients, when more complex timing issues are involved (ventilatory drive and stretch receptors), fastest may not always be best.[2,4–6]

The cycle variable is typically a percentage of the initial inspiratory flow or a pre-set terminal flow. When PSV was introduced, all ventilators cycled the PSV breath when inspiratory flow decayed below 25% of the initial peak flow. Since that time, numerous flow percentages and terminal flows have been used. In the Yamada and Du study,

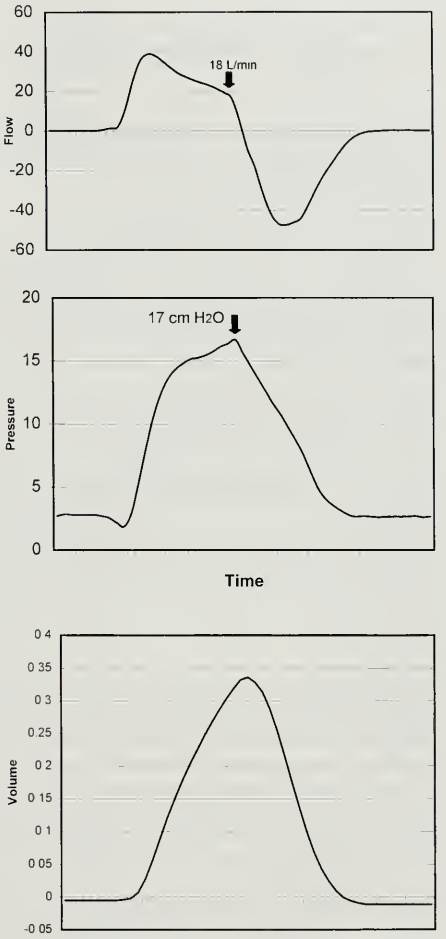

Fig. 1. A single pressure support breath (15 cm H_2O) delivered with the Nellcor Puritan Bennett 7200ae. Arrows on the flow and pressure signals demonstrate that the breath is pressure-cycled. Pressure exceeds the set pressure by >1.5 cm H_2O; upon cycling, the flow is 18 L/min (criterion is 5 L/min).

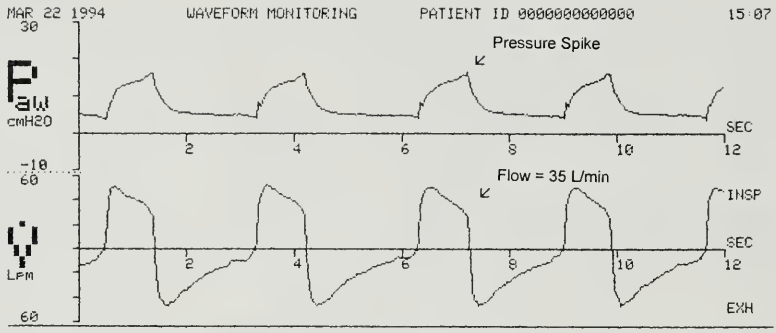

Fig. 2. Pressure and flow tracings during pressure support ventilation, with the Nellcor Puritan Bennett 7200ae demonstrating pressure cycling.

both the Nellcor Puritan Bennett 7200ae (NPB7200ae)* and the Siemens 300 were used. The flow cycle criteria for these ventilators are 5 L/min and 5% of peak flow, respectively. The third ventilator, the Newport Wave E200, uses an automatic adjustment, based on flow and inspiratory time.

The PSV cycle variable can affect patient-ventilator synchrony by causing a neural-mechanical dyssynchrony. This is most often seen as the patient trying to exhale before the ventilator has reached the flow cycle variable (Figs. 1 & 2). This is evidenced by the pressure spike at the end of inspiration and calculation of the flow at which cycling occurs (much higher than 5 L/min). In our experience, this is a common finding during PSV with the NPB7200ae. This prolonged inspiratory time can also cause the patient to attempt an inspiration during the ventilator's inspiratory phase. This is masked by the positive pressure breath, prevents triggering, and further contributes to patient-ventilator synchrony.

As a partial remedy to this problem, manufacturers have developed additional cycle criteria to the PSV breath. For the NPB7200ae, these include an inspiratory time > 5.0 seconds or a pressure 1.5 cm H_2O above the set pressure limit. This allows the patient to exhale and cycle the breath, but requires active exhalation. Each of these cycle variables is functional during every breath. So while we consider the 'simplicity' of a PSV breath, we should consider that each breath may be cycled by any of the 3 variables—flow, time, or pressure.[2]

Where does this leave our perception of the simplicity of PSV? We firmly believe that the adjustment of rise time can improve patient-ventilator interaction. Appropriate trigger setting is also obviously important. We believe the cycle variable is less important in most cases, but in select cases adjusting rise time and flow cycle together may be useful. Theoretically, the clinician could have the choice of setting trigger (flow, pressure, volume, impedance, motion), rise time, and any of 3 cycle variables (flow, time, pressure). In fact, several ventilators have the ability to adjust rise time (Bear 1000, Healthdyne Quantum, Dräger Evita 4 and Dura, Siemens 300, and Hamilton Galileo) and some are able to adjust the flow cycle variable (Bear 3, Hamilton Galileo). Certainly, this greater flexibility will aid in improving patient-ventilator synchrony. Unfortunately, this will come at the expense of 'simplicity.' As an aside, our experience with these techniques is that adjusting rise time is more important than the cycle variable and that changing the cycle variable is rarely useful unless the rise time is first optimized.

The paper by Yamada and Du demonstrates the difference between certain ventilators in the PSV mode. Like any evaluation of a single ventilator function, care should be taken in applying the results to clinical practice. Lung model studies are critical to our understanding of ventilator operation. However, patient-ventilator interactions are much more complex, incorporating neural input, muscle strength, airway caliber, and pulmonary stretch receptors. Whether or not the same results might be seen clinically can only be determined by patient studies.

Lastly, the methodology of reporting 'response time' in this paper is considerably different than what has been done previously.[4,7] With the apparent concern regarding response time shown by clinicians and the representation of response time by manufacturers, perhaps the time has come for experts to define response time. Battling over terminology is a painful, plodding process, but it may help clinicians make more informed decisions related to ventilator purchases. If you are buying a ventilator based on the

*Suppliers of commercial products are identified in the Product Sources section at the end of the text.

reported response time by the manufacturer, you need to re-evaluate priorities.

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PRODUCT SOURCES

Ventilators

Bear 3 and Bear 1000, Thermo Respiratory Group, Palm Springs CA
Evita 4 and Dura, Dräger Inc Critical Care Systems, Chantilly VA
Galileo, Hamilton Medical Inc, Reno NV
Nellcor Puritan Bennett 7200ae, Mallinckrodt Inc, Pleasanton CA
Wave E200, Newport Medical Instruments Inc, Costa Mesa CA
Quantum PSV, Healthdyne Technologies, Marietta GA
Servo 300, Siemens Medical Systems Inc, Iselin NJ

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Effects of Different Pressure Support Termination on Patient-Ventilator Synchrony

Yoshitsugu Yamada MD and Hong-Lin Du MD

BACKGROUND: In pressure support ventilation (PSV), ventilators terminate their flow when the inspiratory flow decays to a certain flow (flow criteria) or when the airway pressure rises a certain amount above the set pressure support level (pressure criteria). There are significant differences among intensive care unit ventilators in regard to these termination criteria. PURPOSE: In this adult simulation study, we investigated if the termination criteria used in intensive care unit ventilators affect the patient-ventilator synchrony in the transition to exhalation. METHODS: A two-compartment lung model was used to simulate spontaneous breathing of the patient with high demand (peak flow of 60 L/min) or low demand (peak flow of 30 L/min). Three ventilators with different flow criteria and pressure criteria in the inspiratory termination were alternately attached to the test lung: the Nellcor Puritan Bennett 7200ae (NPB7200ae), the Siemens Servo300 (SV300), and the Newport Wave E200 (E200). During testing, the PSV level was set at 10 cm H_2O with positive end-expiratory pressure of 0 or 5 cm H_2O. The termination delay time, termination type, inspiratory muscle work, plateau and peak inspiratory pressures, and inspiratory area percent were measured. The tests were conducted at the compliance of 20, 40, and 80 mL/cm H_2O, with a resistor of R5 or R20. RESULTS: In most of the experimental settings, all three ventilators terminated their flow within 0.1 second before or after the end of the 'patient' inspiratory effort. In the 'patient' with long time constant, termination criteria in the SV300 delayed the inspiratory termination by 0.5 second. In all settings in the NPB7200ae and some settings in the E200, the ventilator flow was terminated by the pressure criteria, not by the flow criteria. The NPB7200ae showed pressure undershoot during the first half of the inspiration and required the highest patient work in all settings, especially at high patient demand. In the SV300, the actual support level was higher than the set level. Its peak inspiratory airway pressure was also the highest among the three ventilators. There was a trigger dyssynchrony in the E200 at high demand with high resistance/high compliance. CONCLUSION: In most settings, the termination criteria used in PSV in the three ventilators provided a relatively reasonable patient-ventilator synchrony in the transition to exhalation. The marked delay in the ventilator inspiratory termination may occur under the conditions of long time constant with low demand in the SV300, which resulted mainly from the combination of the inappropriate pressure criteria and flow criteria. [Respir Care 1998;43(12):1048–1057] *Key words: mechanical ventilation, pressure support, work of breathing, ventilators, patient-ventilator synchrony.*

Background

Pressure support ventilation (PSV) has been one of the most frequently applied modes. There are several factors that determine the performance of PSV: ventilator trigger response, pressure rise rate (or slope) upon trigger, and ventilator inspiratory termination timing.[1] Studies on the ventilator trigger response and the pressure rise rate in PSV have clearly shown the importance of their roles in decreasing the patient work of breathing and improving

See The Related Editorial on Page 1045

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patient-ventilator synchrony.[2–6] It has been suggested[7] that ventilator inspiratory termination may also be important: Premature termination may increase inspiratory muscle work, and delayed termination may increase the load on expiratory muscles. In a lung model study, Bunburaphong et al[8] evaluated expiratory delay time in nine noninvasive pressure ventilators together with one intensive care unit (ICU) ventilator. They demonstrated that there were great differences in the termination delay time among the noninvasive pressure ventilators. With regard to ICU ventilators, MacIntyre and Ho[4] evaluated the termination criteria at 25% and 50% of peak flow and found that changing termination criteria in PSV from 50% to 25% of peak flow had minimal effect on the ventilatory pattern or patient-ventilator synchrony in clinically stable patients using a modified Bear-3 ventilator.*

There are two primary methods to terminate the ventilator flow delivery in ICU ventilators during PSV: flow criterion and pressure criterion. As regards the flow or pressure level at which the ventilator flow is terminated, significant differences exist among ICU ventilator manufacturers and even among different model ventilators of the same manufacturer.[9,10] By flow criteria, ventilator flow will be terminated when the inspiratory flow has decayed to a certain flow. This flow can be either a fixed absolute flow (eg, 5 L/min in the Nellcor Puritan Bennett 7200 and 4 L/min in the Infrasonics Adult Star), a fixed rate based on the peak inspiratory flow (eg, 5% of peak inspiratory flow in the Siemens Servo300 and 25% of peak inspiratory flow in the Siemens Servo 900 and Bird 8400ST), or variable termination flow based on both peak inspiratory flow and the elapsed inspiratory time (T_I) (such as in the Newport Wave E200). By pressure criteria, the ventilator flow is terminated when the airway pressure rises a certain amount above the set pressure support level. This pressure criteria above the set pressure level can be +1.5 cm H_2O (in the Nellcor Puritan Bennett 7200 [NPB7200ae]), +2.0 cm H_2O (in the Newport Wave E200 [E200]), +3.0 cm H_2O (in the Siemens Servo 900), or +20 cm H_2O (in the Siemens Servo300 [SV300]). Until now, there has been no objective evidence as to whether these different termination criteria affect the patient-ventilator synchrony. Moreover, it also was not known if the patient-ventilator synchrony using each termination criterion was affected by patient characteristics, because patient mechanics (eg, resistance and compliance) may exert influence on the airway flow change during the inspiratory phase.

*Suppliers of commercial products are identified in the Product Sources section at the end of the text.

Purpose

The purpose of this study was to investigate, under different combinations of respiratory resistance and compliance, whether the termination criteria used by ICU ventilators affect the patient-ventilator synchrony in the transition to exhalation in an adult lung model. The patient-ventilator synchrony was evaluated by the termination delay time (ie, time from the end of the 'patient' inspiratory effort to the end of ventilator inspiratory flow). Since the termination of the inspiration may be affected by a ventilator's control of the flow delivery during inspiration with the same termination criteria, the performance characteristics of the ventilators during the inspiratory phase were evaluated as well. The NPB7200ae, the SV300, and the E200 were used to represent ventilators with different termination criteria.

Methods

Model

Spontaneous breathing was simulated using a two-compartment mechanical lung model (Michigan, TTL model 1600) (Fig. 1). The left side of the lung model was connected to the tested ventilator; the right side was connected to and driven by a Bear-5 ventilator using a sinusoidal flow wave pattern. The model in this study differs from that used by other researchers,[11,12] in that it used a metal connector to completely connect both sides of the model. This connection allowed the two compartments to behave like compliances in series. Because of this connection, if the flow termination of the tested ventilator comes after the end of the inspiration of the driving lung, the elastic recoil force from the driving lung impacts the tested lung and causes an airway pressure elevation. This model simulates the interactive relationship between a ventilator and a patient who does not exhibit active expiratory effort. When the compliance of the driving side lung is set to the chest wall compliance, the pressure in the driving side lung during the driving phase can be taken as the inspiratory muscle pressure. The integration of the volume change and pressure change during the driving phase is taken as the work of inspiratory muscles (Wmus).[13,14] After the driving phase, the pressure or flow information of the driving side in this model cannot be used for analysis of the Wmus because the driving compartment at this time communicates with the atmosphere through the open exhalation valve of the driving ventilator.

Setup

The compliance of the driving lung was set at 200 mL/cm H_2O to simulate chest wall compliance. A hot wire flow transducer (Minato, Model RF-L) and a pressure trans-

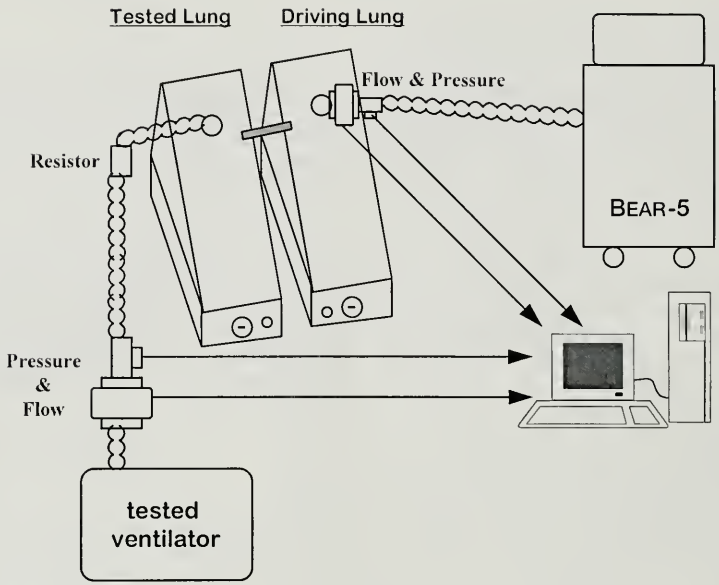

Fig. 1. Schematic representation of the lung model.

ducer (Heise, 901A) were connected to the inlet of the driving lung. The left lung (tested lung) was connected to each of the tested ventilators through a standard adult breathing circuit with no humidifier attached (circuit compliance = 0.98 mL/cm H_2O). The pressure and flow at the airway opening were measured by the same types of transducers that were used at the driving side. The signals of pressure and flow transducers at both the driving side and tested side were digitized at 100 Hz and recorded on a computer recorder (Data Translation, DT2831). To simulate the respiratory system resistance, a parabolic resistor of R5 or R20 was placed between the tested lung and the breathing circuit. The compliance of the tested lung was adjusted to 20, 40, or 80 (C20, C40, or C80) mL/cm H_2O. With the T_I set to 1.0 second, the peak flow of the BEAR-5 ventilator was adjusted to provide the peak inspiratory flow of 30 L/min and 60 L/min at the airway opening of the tested side when the tested lung was not connected to a ventilator. These flow rates simulated low and high patient inspiratory efforts. During the evaluation of the tested ventilators, the 3 tested ventilators set in the spontaneous mode were connected to the tested lung alternately. The positive end-expiratory pressure (PEEP) was set at 0 or 5 cm H_2O and pressure support was set at 10 cm H_2O. Pressure trigger of -0.5 cm H_2O was used in all 3 ventilators. In the SV300, the inspiratory rise time was adjusted to 1%. In the E200, the bias flow was set at 5 L/min, as recommended by its operating manual.[15] The 4 transducers used in the study (2 for pressure and 2 for flow) were calibrated immediately before the experiment with a calibration analyzer (Allied Healthcare Products, RT200).

Measurements and Data Analysis

The following parameters were measured from the computer records: termination delay time and termination type, Wmus expressed as J/L during the driving phase at the driving side, plateau and peak inspiratory pressures at the tested side, and inspiratory area percent (Area-I%) of the pressure at the tested side.

The termination delay time was defined as the time between the end of the inspiration of the BEAR-5 and the return of the inspiratory flow of the tested ventilator to zero (Fig. 2). The end of the inspiration of the BEAR-5 was calculated as follows: The inspiratory onset of the BEAR-5 during each test was read from the flow waveform of the driving compartment; the T_I of the BEAR-5 was measured from the flow waveform of the driving compartment when no tested ventilator was attached to the tested lung compartment (the variation of the T_I of the BEAR-5 was confirmed to be $\leq$ 20 millisecond in all experimental settings in the preliminary experiments); and timing of the end of the inspiration of the BEAR-5 when a tested ventilator was being evaluated was then BEAR-5's inspiratory onset tim-

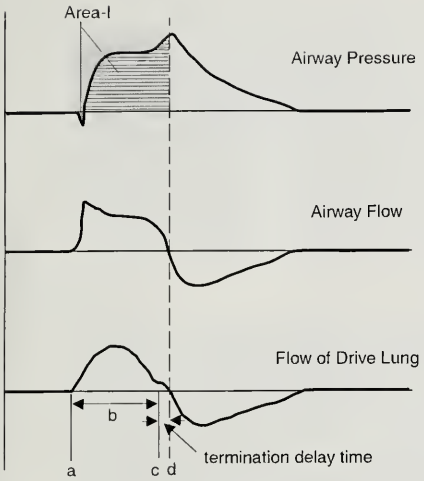

Fig. 2. Calculations of the termination delay time and the inspiratory area percent of airway pressure. The termination delay is defined as the time between the end of the inspiration of the drive ventilator (c) and the return of the inspiratory flow of the tested ventilator to zero (d). The mandatory inspiration of the drive ventilator starts at "a" and lasts for the duration of "b," which is taken when no ventilator is connected to the tested lung. The inspiratory area percent of airway pressure is the ratio of the line-shaded areas (Area-I, the areas of the pressure-time tracing above and below baseline during the inspiration) to the dot-shaded rectangle area (ideal area).

ing plus Bear-5's T_I. To identify whether the ventilator flow was terminated by the flow criterion or pressure criterion, the time point when the airway pressure at the tested side reached the pressure criterion level was read. The pressure criterion level was taken as 11.5 cm H_2O above PEEP in the NPB7200ae, 30.0 cm H_2O above PEEP in the SV300, and 12.0 cm H_2O above PEEP in the E200.[9,10,15] The patient airway flow at this time point was measured and compared with the flow criterion. If it was higher than the flow criterion, the inspiration was thought to be terminated by the pressure criterion; otherwise, the inspiration was considered to be terminated by the flow criterion. The inspiration was always considered to be terminated by the flow criterion if the airway pressure never reached the pressure criterion level during inspiration.

The Wmus was calculated as the integral of the pressure at the driving side with regard to the volume at the tested side during the driving phase. The volume at the tested side was obtained by integrating the flow signal of the tested side over time. The intention of using the volume at the tested side (instead of using the volume at the driving side) in the calculation of the Wmus was to simulate a clinical situation and to eliminate the effect of the compressed volume in the model. The plateau inspiratory airway pressure at the tested side was read if the airway pressure did not change 0.5 cm H_2O within a 150-millisecond period during the inspiratory phase. The Area-I% was calculated using the method introduced by Bunburaphong et al.[8] The Area-I% was the ratio of the area of the pressure-time tracing above and below baseline during the driving phase at the tested side to the ideal area (Fig. 2). The ideal area was defined as the rectangle created by T_I and the maximal pressure at the tested side above the baseline pressure.

All pressure values in this study are presented as values above PEEP. Three breaths were analyzed for each experimental setting after a 2-min stabilization period. Because all parameters among the three breaths showed negligible variation, only mean values are presented in this report.

Results

Ventilator Inspiratory Termination (Table 1)

All three ventilators terminated their flow delivery within 0.1 second before or after 'patient'-stopped inspiratory effort in most experimental settings. The termination was delayed by 0.5 seconds in the SV300 in the 'patient' with long time constant (R20, C80) and low inspiratory effort (peak inspiratory flow = 30 L/min) (Fig. 3). The inspiration in the NPB7200ae was always terminated by its pressure criterion, while inspiration was terminated by the flow criterion in the SV300. In the E200, if the 'patient' demand was low, inspiration was terminated by its flow criterion, but it was terminated either by its flow criterion or by its pressure criterion in the high-demand 'patient.' The termination delay is not consistently affected by PEEP; however, administration of PEEP slightly prolonged the termination delay time when airway resistance was high (R20) in most of the settings in all ventilators.

The Work of the Inspiratory Muscles (Table 2)

The Wmus in the NPB7200ae was always higher than that in the other 2 ventilators. The Wmus in the SV300 was the lowest among the 3 ventilators, although the differences between the SV300 and the E200 were negligible.

Plateau Inspiratory Pressure, Peak Inspiratory Pressure, and Inspiratory Area Percent (Tables 3–5)

The NPB7200ae consistently displayed an undershoot of airway pressure during the first half of inspiration, especially in high-demand conditions (peak inspiratory flow = 60 L/min) (Figs. 3 & 4). The significant pressure undershoot waveform in high-demand conditions in the NPB7200ae did not allow á stable plateau pressure segment

Table 1. Termination Delay Time (in Seconds) for Three Pressure Support Ventilators Set at Positive End-Expiratory Pressure of 0 or 5 cm H_2O (PEEP-0 or PEEP-5) and Tested at Compliance of 20, 40, or 80 (C20, C40, C80) and Parabolic Resistance of 5 or 20 (R5, R20).

	High Demand (60 L/min)			Low Demand (30 L/min)		
	NPB7200	SV300	E200	NPB7200	SV300	E200
PEEP-0						
R5, C80	0.05(P)	0.09	0.04(P)	0.02(P)	0.06	−0.05
R5, C40	0.03(P)	0.05	0.01	−0.02(P)	0.01	−0.06
R5, C20	−0.04(P)	0.01	−0.01	0.03(P)	0.07	−0.02
R20, C80	0.06(P)	0.10	0.05(P)	0.07(P)	0.56	0.02
R20, C40	0.07(P)	0.10	0.09(P)	0.07(P)	0.13	0.00
R20, C20	0.04(P)	0.05	0.04	0.03(P)	0.04	0.01
PEEP-5						
R5, C80	0.00(P)	0.06	−0.04	0.01(P)	0.09	0.04
R5, C40	−0.03(P)	0.05	0.00	0.00(P)	0.08	0.02
R5, C20	−0.04(P)	0.04	−0.03	−0.03(P)	0.02	−0.04
R20, C80	0.14(P)	0.19	0.11(P)	0.04(P)	0.57	0.04
R20, C40	0.10(P)	0.13	0.09(P)	0.04(P)	0.14	0.02
R20, C20	0.05(P)	0.08	0.05	0.06(P)	0.07	0.02

A two-compartment lung model was used to simulate spontaneous breathing of patients with high- or low-demand peak flow. Positive values represent delayed termination time, negative values represent premature termination time. Termination was pressure-activated (indicated by (P)) or flow-activated. See Methods for details. Ventilators: Nellcor Puritan Bennett 7200ae (NPB7200), Siemens 300 (SV300), Newport Wave E200 (E200).

meeting our plateau pressure definition. When comparing the plateau inspiratory pressure with the target pressure level (10 cm H_2O above PEEP), the plateau pressure was 1–2 cm H_2O lower in the NPB7200ae and 1–2 cm H_2O higher in the SV300 than the target pressure. The undershoot airway pressure in the NPB7200ae also resulted in the lowest Area-I % among the 3 ventilators. In the condition of high demand (peak inspiratory flow = 60 L/min) with long time constant (R20, C80), the E200 showed a double-cycled pressure waveform because of the initial pressure overshoot (Fig. 4). This double-cycled waveform caused a low Area-I% in this condition in the E200. Similar to the differences of plateau pressure among the three ventilators, the peak inspiratory airway pressure was always the highest in the SV300, followed by the E200 and then the NPB7200ae. The peak inspiratory pressure became elevated as the resistance increased and the compliance decreased. It was as high as 12 cm H_2O above the target pressure in R20, C20 with high-demand condition in the SV300.

Discussion

Our results demonstrated that in most of the experimental settings, all 3 ventilators that we tested terminated their flow in PSV within 0.1 second before or after the end of the 'patient' inspiratory effort, suggesting a relatively reasonable patient-ventilator synchrony in the transition to exhalation. In the low-demand 'patient' with long time constant (R20, C80), termination criteria in the SV300 delayed the ventilator inspiratory termination by 0.5 seconds (Table 1, Fig. 3). In all settings in the NPB7200ae and in some settings in the E200, inspiration was terminated by the pressure criteria instead of flow criteria.

In order for airway pressure to remain at the target level during the inspiration of PSV, ventilators decrease their flow as the patient effort decreases. With an ideal pressure control system, in order to maintain the target pressure level, the ventilator flow would be 0 when the patient completely stops his effort. Therefore, the flow criterion of the inspiratory termination in an ideal pressure control system would be set close to 0 L/min. In reality, however, there are inherent delays in the pressure control feedback loop, and the pressure control algorithm more or less lacks precision in all ventilators. As a result, in order to terminate their flow to synchronize with the patient, commercial ventilators are designed to have a termination flow of slightly higher than 0 L/min. The ventilators are designed to terminate their flow when the inspiratory flow drops to either a fixed flow (eg, 5 L/min in the NPB7200ae), a percentage of the peak delivered flow (eg, 5% in the SV300), or a variable termination flow (eg, in the E200).

In addition to termination of flow according to these flow criteria, the ventilators also terminate their flow by the pressure criteria (ie, when airway pressure reaches 1.5 cm H_2O above the target pressure level in the NPB7200ae, 20 cm H_2O above the target pressure level in the SV300,

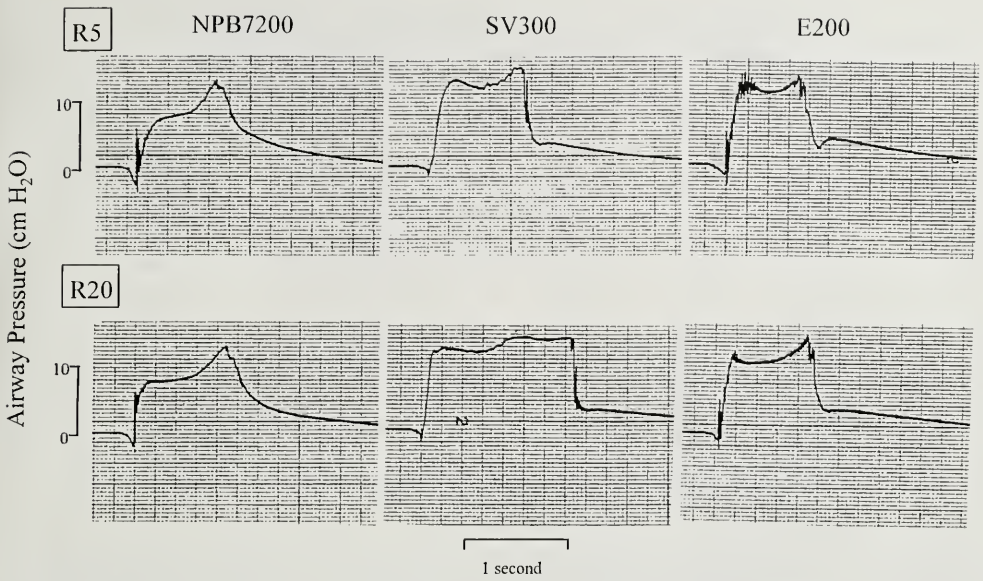

Fig. 3. The pressure waveforms in low demand. Patient demand: 30 L/min; compliance: 80 mL/cm H_2O; resistance: R5 (upper) and R20 (lower). NPB7200 = Nellcor Puritan Bennett 7200ae; SV300 = Servo 300; E200 = Wave E200.

or 2.0 cm H_2O above the target pressure level in the E200). These pressure criteria serve as a backup measure to the flow criteria. The results in our study showed that the pressure criteria in the SV300 (20 cm H_2O above the target pressure) did not activate termination in any setting: The ventilator flow was terminated by the flow criterion. This may partly explain why the peak inspiratory airway pressure in the SV300 can be as high as 12 cm H_2O above the target pressure (Table 4). The fact that inspiration in the NPB7200ae was always terminated by the pressure criterion suggests that the flow criterion of 5 L/min used in the NPB7200ae is not high enough to terminate its flow at the proper time at the applied settings. In other words, the flow criterion of 5 L/min in the NPB7200ae has not functioned in the ventilator inspiratory termination. Because the termination in the NPB7200ae was not markedly delayed even though the ventilator flow was always terminated by the pressure criterion, it can be inferred that the pressure criterion in the SV300 is the major reason for the significant termination delay that occurred in the SV300. The termination delay in the SV300 may also be attributed to the lower flow criterion because the highest peak flow recorded in the SV300 study was 76 L/min (which was converted to 3.8 L/min of flow criterion in ventilator inspiratory termination).

In the E200, ventilator flow was terminated by the flow criteria without significant delay or prematurely in low-demand conditions. This indicates that relating the flow criteria with the elapsed T_I in addition to peak flow may result in better patient-ventilator synchrony than using only peak flow. In the E200, termination is based on the following equation: termination flow = $(\alpha + \beta \times TI) \times PF^{\gamma}$, where TI is the elapsed T_I from the onset of the ventilator flow, PF is the peak inspiratory flow, and α, β, and γ are constants.† With this flow criterion, the longer the elapsed T_I, the higher the termination flow criteria, and vice versa. This might compensate the slower decay of the inspiratory flow at long time constant and low demand. In the high demand, this compensation with the elapsed T_I is not enough, as demonstrated by the pressure-cycled breath at high demand and high resistance in the E200.

Jubran and co-workers have studied the effect of PSV in chronic obstructive pulmonary disease patients.[16] In their study, they ventilated chronic obstructive pulmonary disease patients with PSV by use of the Servo 900C ventilator. As a result, the patients with higher time constants displayed lower bounds of expiratory pressure time prod-

†Personal communication, Cyndy Miller RRT, Newport Medical Instruments Inc, Costa Mesa CA.

Table 2. Inspiratory Muscle Work (in J/L) for Three Pressure Support Ventilators Set at Positive End-Expiratory Pressure of 0 or 5 cm H_2O (PEEP-0 or PEEP-5) and Tested at Compliance of 20, 40, or 80 (C20, C40, C80) and Parabolic Resistance of 5 or 20 (R5, R20).

	High Demand (60 L/min)			Low Demand (30 L/min)		
	NPB7200	SV300	E200	NPB7200	SV300	E200
PEEP-0						
R5, C80	1.14	0.87	0.89	0.24	0.05	0.08
R5, C40	1.51	1.25	1.32	0.46	0.25	0.30
R5, C20	3.03	2.78	2.88	1.37	1.03	1.08
R20, C80	2.63	2.33	2.63	0.52	0.30	0.35
R20, C40	3.13	3.00	3.10	0.78	0.55	0.66
R20, C20	3.67	3.53	3.61	1.69	1.48	1.49
PEEP-5						
R5, C80	0.92	0.68	0.64	0.07	0.02	0.03
R5, C40	1.33	1.09	1.06	0.28	0.18	0.21
R5, C20	2.82	2.61	2.61	1.08	0.81	0.94
R20, C80	2.75	2.51	2.71	0.37	0.23	0.32
R20, C40	2.95	2.85	2.90	0.54	0.42	0.51
R20, C20	3.61	3.46	3.57	1.38	1.24	1.29

A two-compartment lung model was used to simulate spontaneous breathing of patients with high- or low-demand peak flow. Ventilators: Nellcor Puritan Bennett 7200ae (NPB7200), Siemens 300 (SV300), Newport Wave E200 (E200).

uct before the cessation of the inspiratory flow, suggesting expiratory muscle recruitment while the ventilator was still inflating the thorax. Because the Servo900C utilizes a flow criterion of 25% of the peak flow and a pressure criterion of 3 cm H_2O,[9,10] the ventilator inspiratory termination should be earlier using the Servo900C than the SV300. This means that the expiratory muscle work would be higher if the SV300 was used in these patients. The significant delay in the ventilator inspiratory termination will also shorten expiratory time and may exacerbate auto-PEEP, which frequently is an important clinical issue in these patients.[17]

In addition to the flow criterion and pressure criterion, ICU ventilators also have a termination criterion based on maximum T_I in order to protect patients in case of a massive circuit leak. The ventilators will terminate their flow if the T_I reaches 3.0 seconds in the NPB7200ae and the E200 or 80% of one breath interval in the SV300.[9,10,15] Because there were no patient circuit leaks during this study, there were no breaths that lasted long enough to be terminated by this criterion.

Some newly released ICU ventilators (eg, NPB 840, Hamilton Galileo) allow manual selection of the termination flow percentage (flow criterion). This is designed to help clinicians fine-tune the ventilator inspiratory termination for individual patients. However, the setting of the termination flow percentage is difficult with visual observation of the airway pressure waveform at bedside and may be impossible when waveform analysis is unavailable.[8] Moreover, the patient effort and mechanics may change over time, which necessitates frequent adjustments by clinicians. Automatic variable termination criterion combined with appropriate pressure criterion seems more user friendly and may sufficiently improve the patient-ventilator synchrony.

Table 3. Plateau Airway Pressure (in cm H_2O) for Three Pressure Support Ventilators Set at Positive End-Expiratory Pressure of 0 or 5 cm H_2O (PEEP-0 or PEEP-5) and Tested at Compliance of 20, 40, or 80 (C20, C40, C80) and Parabolic Resistance of 5 or 20 (R5, R20).

	Low Demand (30 L/min)		
	NPB7200	SV300	E200
PEEP-0			
R5, C80	8.4	12.0	10.8
R5, C40	8.5	11.5	10.2
R5, C20	8.5	11.4	10.2
R20, C80	8.4	12.0	10.5
R20, C40	8.4	11.7	10.7
R20, C20	8.1	11.4	10.8
PEEP-5			
R5, C80	8.5	11.5	10.4
R5, C40	9.0	11.4	10.6
R5, C20	8.6	11.1	10.5
R20, C80	8.4	11.2	10.7
R20, C40	8.5	11.8	10.2
R20, C20	8.4	10.8	10.3

Lung model simulated spontaneous breathing of patients with low-demand peak flow. All pressures are those above PEEP level. Ventilators: Nellcor Puritan Bennett 7200ae (NPB7200), Siemens 300 (SV300), Newport Wave E200 (E200).

Table 4. Peak Inspiratory Airway Pressure (in cm H_2O) for Three Pressure Support Ventilators Set at Positive End-Expiratory Pressure of 0 or 5 cm H_2O (PEEP-0 or PEEP-5) and Tested at Compliance of 20, 40, or 80 (C20, C40, C80) and Parabolic Resistance of 5 or 20 (R5, R20).

	High Demand (60 L/min)			Low Demand (30 L/min)		
	NPB7200	SV300	E200	NPB7200	SV300	E200
PEEP-0						
R5, C80	11	13	11	11	13	12
R5, C40	12	14	12	11	13	12
R5, C20	13	14	12	11	13	13
R20, C80	11	16	13	11	13	12
R20, C40	14	19	17	12	14	12
R20, C20	14	22	16	11	18	12
PEEP-5						
R5, C80	10	14	12	12	13	12
R5, C40	12	15	12	12	13	13
R5, C20	13	15	12	12	14	13
R20, C80	12	17	13	12	13	13
R20, C40	13	20	13	12	14	12
R20, C20	14	22	15	12	18	13

A two-compartment lung model was used to simulate spontaneous breathing of patients with high- or low-demand peak flow. All pressures are those above PEEP level. Ventilators: Nellcor Puritan Bennett 7200ae (NPB7200), Siemens 300 (SV300), Newport Wave E200 (E200).

Table 5. Inspiratory Area Percent (Area-I%) of Airway Pressure for Three Pressure Support Ventilators Set at Positive End-Expiratory Pressure of 0 or 5 cm H_2O (PEEP-0 or PEEP-5) and Tested at Compliance of 20, 40, or 80 (C20, C40, C80) and Parabolic Resistance of 5 or 20 (R5, R20).

	High Demand (60 L/min)			Low Demand (30 L/min)		
	NPB7200	SV300	E200	NPB7200	SV300	E200
PEEP-0						
R5, C80	33	54	55	55	71	69
R5, C40	39	56	60	60	67	70
R5, C20	43	56	61	57	66	67
R20, C80	39	65	26	62	73	72
R20, C40	35	69	70	59	73	72
R20, C20	46	66	69	57	70	71
PEEP-5						
R5, C80	43	54	61	63	65	65
R5, C40	48	56	62	59	65	62
R5, C20	47	54	65	65	71	67
R20, C80	38	59	36	64	72	66
R20, C40	42	61	70	62	72	66
R20, C20	52	66	70	64	71	64

A two-compartment lung model was used to simulate spontaneous breathing of patients with high- or low-demand peak flow. Ventilators: Nellcor Puritan Bennett 7200ae (NPB7200), Siemens 300 (SV300), Newport Wave E200 (E200).

The Wmus is a function of the trigger delay, actual pressure support level, and termination synchrony (premature termination or delayed termination). In this study, the calculation of the Wmus used only the pressure and volume of the driving phase; therefore, the delayed termination will not affect the appropriateness of the calculation of the Wmus. While there was not marked premature termination (Table 1) and the Wmus corresponding to the trigger phase only accounts for a minimal part of the total Wmus (data not shown), the difference in the Wmus mainly represents the difference of the inspiratory output of the ventilators.

Our results showed that the Wmus (J/L) was the highest in the NPB7200ae among all tested ventilators. This is the result of the insufficient initial flow delivery from the NPB7200ae. The insufficient initial flow delivery also

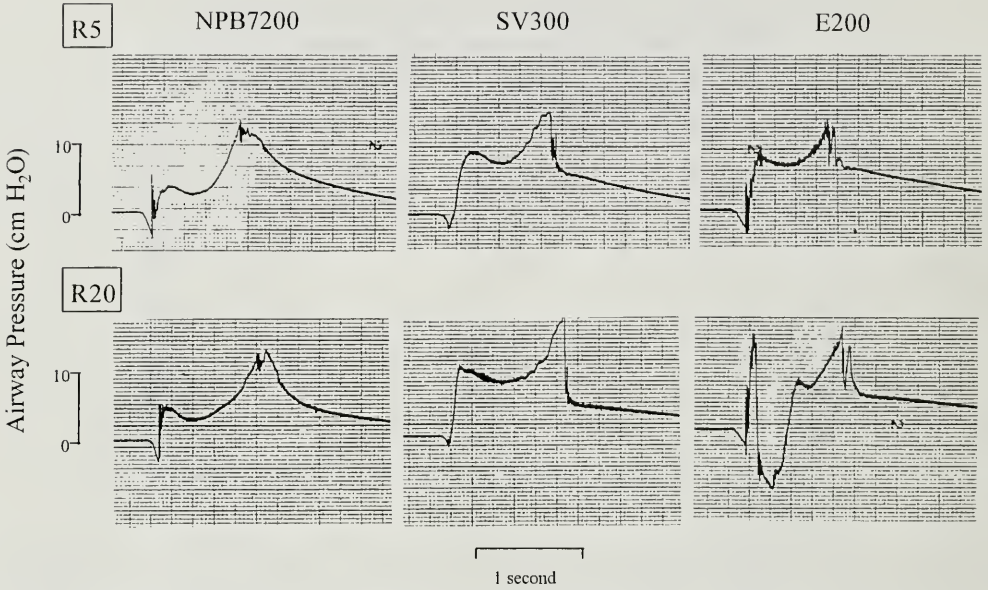

Fig. 4. The pressure waveforms in high demand. Patient demand: 60 L/min; Compliance: 80 mL/cmH2O; resistance: R5 (upper) and R20 (lower). NPB7200 = Nellcor Puritan Bennett 7200ae; SV300 = Servo 300; E200 = Wave E200.

causes pressure undershoot during the first half of the inspiratory phase.[6,18] This is consistent with the finding that the Area-1% in the NPB7200ae was also markedly lower than that in the other two ventilators. On the other hand, the Wmus in the SV300 was always the least among all tested ventilators due to the higher actual support pressure level. Although the pressure support level in the three ventilators was set at 10 cm H_2O, the actual plateau pressure was 1–2 cm H_2O higher than the set pressure support level in the SV300, suggesting excessive support. We set inspiratory rise time to 1% in the SV300 in order to shorten the negative airway pressure period because in our preliminary experiments we found a longer negative airway pressure period at a higher inspiratory rise time. Meanwhile, this fast pressurization did not cause pressure overshoot even in high resistance/low compliance conditions. The significant high peak inspiratory airway pressure in the SV300 appeared around the end, not the start, of inspiration. The high peak inspiratory airway pressure resulted from high pressure criterion (+20 cm H_2O above the target pressure) and low flow criterion (5% of peak flow). The trigger dyssynchrony in the E200 in high demand with long time constant conditions resulted from the initial pressure overshoot, suggesting the insufficient initial flow control algorithm under this condition.

Since our data are based on a lung model, careful consideration should be taken when extrapolating it to the clinical setting. In addition, there are several limitations in the design of our study. First, the 'patient' cannot actively exhale in our lung model. In clinical sites, active exhalation from the patient expiratory muscle activity may cause inspiratory flow decline quicker than it did in this study. This may shorten the ventilator inspiratory termination delay time; however, it would be at the cost of the patient expiratory muscle work.[16] Second, the pressure and flow signals used for analyses in this study were measured at the place between the tested ventilator and the tested lung. The flow and pressure signals used for the control of the flow delivery in the 3 ventilators are actually measured within ventilators, except that in the E200, the pressure is measured at the patient circuit proximal wye connector. This difference in the measurement locations may introduce some degree of error due to the breathing circuit. Last, we only simulated the patient T_I of 1.0 second. Shorter or longer patient T_I may change the termination delay time quantitatively. These limitations should be taken into account when interpreting the results of this study for clinical purposes. It should also be noted that the patient-ventilator synchrony in the transition to exhalation may not be solely the result of termination criteria. The timing

of flow termination in a ventilator is also related to that ventilator's inspiratory output. Therefore, the results in this study may not be directly extrapolated to other ventilators using the same termination criteria.

Conclusion

In conclusion, the termination criteria used in PSV in the 3 ventilators provided a relatively reasonable patient-ventilator synchrony in the transition to exhalation in most settings. The marked delay in the ventilator inspiratory termination may occur under the conditions of long time constant with low demand in the SV300, which resulted mainly from the combination of the inappropriate pressure criteria and flow criteria. Although the pressure criteria are designed as a backup measure to the flow criteria in the inspiratory termination, it consistently functions as a primary mechanism in the NPB7200ae.

PRODUCT SOURCES

Ventilators

Nellcor Puritan Bennett 7200ae, Mallinckrodt Inc, Pleasanton CA

Servo 300, Siemens Medical Systems Inc, Iselin NJ

Wave E200, Newport Medical Instruments Inc, Costa Mesa CA

Bear-5, Thermo Respiratory Group, Palm Springs, CA

Flow Transducer

Model RF-L, Minato Medical Science Co. Ltd., Osaka, Japan

Pressure Transducer

Heise 901A, Dresser Industries Inc, Stratford CT

Data Acquisition System

DT2831 and Global Lab, Data Translation Inc, Marlborough MA

Lung Model

TTL Model 1600, Michigan Instruments Inc, Grand Rapids MI

Calibration Analyzer

RT-200, Allied Healthcare Products, St Louis MO

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Evaluation of the Normal Inspiratory Flow-Volume Curve

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INTRODUCTION: The normal inspiratory flow-volume (FV) curve has not been extensively characterized. Acceptability criteria have been proposed but not thoroughly evaluated, and formal recommendations have not been published. This study was done to further characterize the inspiratory FV curve and to evaluate the provisional guidelines in a population of normal subjects. METHODS: The design for the study is a retrospective review of pulmonary function reports. The setting for the study was a university teaching hospital and tertiary care referral center. Subjects (patients) were ≥ 18 years old, had no pulmonary symptoms or disease, and had a normal expiratory spirometry between December 1993 and December 1994. RESULTS: One hundred twenty-one studies were evaluated. There were 91 men in the group, with a mean age of 52.1 years (± 16.7 years; range, 19–92 years). In 62.8% (n = 76) of cases, the maximum inspiratory flow (MIF) did not occur during the 'best effort' expiratory curve (largest sum of forced expiratory volume in one second + forced expiratory vital capacity [FVC]). The best forced inspiratory flow at 50% of vital capacity (FIF_{50}) was ≥ 95% of the MIF (on same effort) in only 62.8% of cases (n = 76). The forced inspiratory vital capacity (FIVC) on any effort was ≥ FVC in only 44.6% of subjects (n = 54). The FIVC was ≥ 90% of the FVC on the effort containing the best MIF in 87.6% of cases (n = 106). The inspiratory FV curve containing the largest MIF was parabolic with one inflection point in only 53.1% of cases in which there was agreement in the interpretation of curve shape between 2 of the authors. CONCLUSIONS: Evaluation of inspiratory FV data from only the best effort expiratory curve misses a significant portion of maximal MIF and FIF_{50} values. Therefore, spirometry equipment should be designed to allow the technician to choose the best inspiratory FV loop. On the basis of our findings, FIF_{50} ≥ 95% MIF, FIVC ≥ FVC, or a parabolic shape with only one inflection point are not optimal criteria for a normal or acceptable inspiratory FV curve when the inspiratory effort is performed immediately following a forced expiratory maneuver. However, FIVC ≥ 90% FVC may be useful as a criterion of acceptability. Last, it is possible that recording inspiratory and forced expiratory maneuvers separately will result in loops that are more consistent with expectations. Further evaluation using larger populations is needed before definitive recommendations can be made. [Respir Care 1998;43(12):1058–1063] *Key words: Pulmonary function testing, physiology, flow-volume loop, inspiration, normal values.*

Introduction

Although the expiratory flow-volume (FV) curve receives more attention during interpretation of forced spirometry, the inspiratory loop provides useful information. In their early research on obstructing lesions of the larynx and trachea, Miller and Hyatt[1,2] recognized and described the importance of the inspiratory FV loop in diagnosing upper airway obstruction. Since then, the inspiratory loop has been evaluated with increasing frequency. The inspira-

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tory loop has been reported to be abnormal in patients with vocal cord dysfunction[3] and sleep-disordered breathing[4] and to correlate with airway hyperreactivity.[5] An abnormal inspiratory FV loop is also considered an indication to avoid general anesthesia in adults with anterior mediastinal masses;[6] however, this recommendation is based on anecdotal evidence.[7]

Extensive guidelines describing the adequacy of forced expiratory spirometry exist.[8–11] This is not true for the inspiratory FV curve. Although 'abnormal' curves have been described in the above-mentioned disease processes, there has not been a thorough evaluation of what constitutes a satisfactory test and 'normal' results; however, provisional guidelines have been proposed.[12,13] As Ewald et al[13] state, ". . . the most significant factor limiting the interpretation of . . . inspiratory FV curve(s) . . . is absence of uniform criteria that define an adequate inspiratory FV curve performance." Therefore, we undertook this study to further describe a normal inspiratory FV curve and to evaluate the proposed guidelines in a group of normal subjects.

Methods

Procedure and Data Collection

All available screening spirometries and accompanying pre-spirometry questionnaires (~4800) performed in the Walter Reed Army Medical Center pulmonary function testing laboratory between 1 December 1993 and 1 December 1994 were reviewed. Initially, all studies for patients who met the following inclusion criteria were collected: beneficiaries of the military health care system who were ≥ 18 years of age, patients with no reported history of pulmonary symptoms or pulmonary disease on a pre-spirometry questionnaire, and patients with no pulmonary or systemic diseases commonly involving the lung noted on the request by the referring health care provider. From this subgroup, only studies for patients having ratios of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) (FEV_1/FVC) within the 95% normative range were retained for final analysis. Normal values were derived from Crapo et al,[14] and corrections for race were made in accordance with published guidelines.[15] All testing followed published guidelines for performance of pulmonary function tests [8–11] using standard pulmonary function equipment (Cybermedic Inc, Boulder CO, and Sensormedics Corp, Yorba Linda CA). In one case, two different sets of spirometry were performed on the same individual within the study period, but only the first set of results was used in the analysis.

For each spirometric study, the computer program used by our pulmonary function equipment printed the 3 best trials (from up to 8 efforts), as determined on the basis of the largest sum of FVC + FEV_1. These 3 trials and corresponding FV curves made up the printed report for each subject. The best trial and accompanying expiratory and inspiratory values were printed in Column 1, the values from the next best trial were printed in Column 2, and the values from the third best trial were printed in Column 3. Each column contained at least the following evaluated variables: FVC, FEV_1, FEV_1/FVC, forced inspiratory vital capacity (FIVC), forced inspiratory volume in the first second of inspiration (FIV_1), maximum inspiratory flow (MIF), and forced inspiratory flow at 50% of vital capacity (FIF_{50}). To determine if the largest values occurred together on the same trial, we ranked raw data across the three trials for each variable (largest [No. 1] to smallest [No. 3]). For example, a subject with an FEV_1 of 2.13 L, 2.20 L, and 2.10 L in Columns 1, 2, and 3 would be ranked as 2, 1, 3.

Data Analysis

We evaluated the characteristics of normal inspiratory FV in three ways: (1) We examined the relationship between the inspiratory flow variables (FIVC, FIV_1, MIF, FIF_{50}) by determining how often (using both raw numbers and percentages) two variables occurred together, and we examined the relationship between the inspiratory variable FIVC and the expiratory variable FVC, again using raw numbers and percentages; (2) we evaluated the agreement between each of the pulmonary function variables, on the basis of their order of magnitude across the 3 printed trials (cases in which equal values occurred on 2 or 3 of the trials [41 of 957 triplets, 4.3%]) were not included in this part of the analysis; and (3) we evaluated the shape of the inspiratory FV curve. The choices for shape of the inspiratory curve were simplified to parabolic and one inflection point, parabolic and more than one inflection point, flattened and smooth, flattened and jagged, and 'other' to minimize observer bias and subjectivity and to increase the accuracy of classification. The shape of the inspiratory FV curve was independently evaluated by 2 of the authors (OH and AS), who were blinded to each other's evaluations.

Data are expressed as mean percentages and the 95% confidence interval (CI). Differences between sex, race, or smoking status for each pulmonary function variable were evaluated using the two-tailed Fisher's exact test. Ken-

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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dall's tau-b and Spearman's correlation coefficient were used to determine the correlation between pulmonary function variables. Two-sided p values < 0.05 were considered statistically significant.

Results

One hundred twenty-one studies were included in the final analysis. There were 91 men (75.2%) and 30 women (24.8%) in this group, with a mean age of 52.1 (± 16.7 years; range, 19–92 years). Studies were done on 97 white patients (80.2%), 23 African-American patients (19%), and 1 Asian-American patient (0.8%). Spirometries were performed on 42 nonsmokers (34.7%), 21 current smokers (17.4%), and 58 ex-smokers (47.9%). Spirometry was performed preoperatively in 79 cases (65.3%), as part of routine occupational health screening in 25 cases (20.7%), and for other reasons in 17 cases (14.0%). There were no statistically significant differences between sex, race, or smoking status for any of the evaluated variables except parabolic FV loops, as explained below.

In 45 studies (37.2%; 95% CI = 28.7%–46.5%), the largest MIF occurred on the 'best effort' expiratory curve (largest sum of FEV_1 and FVC). In 42 studies (34.7%; 95% CI = 26.4%–44.0%), the largest FIF_{50} occurred on the best effort expiratory curve. Relationships between other inspiratory pulmonary function variables are shown in Table 1. The observed relationships between FIVC and FVC are shown on Table 2. There was significant correlation between MIF and FIF_{50} and both MIF and FIF_{50} and the inspiratory FV curve with the largest combined FIVC, MIF, and FIF_{50} (Table 3). To evaluate reproducibility, we chose variables related to those used in the expiratory FV curve. We found that the largest FIV_1 or FIVC were within 5% of the second largest values in only 84 (76.4%; 95% CI = 67.2%–83.8%) of 110 cases.

There was agreement between 2 of the authors regarding the shape of the inspiratory FV curve in 98 studies (81.0%). In the concordant studies, the inspiratory FV loop containing the largest MIF was parabolic with one inflection point in 52 cases (53.1%; 95% CI = 42.8%–63.1%) and parabolic with 2 inflection points in 29 studies (29.6%; 95% CI = 21.0%–39.8%) (Fig. 1). There was a statistically larger percentage of women (21/27, 77.8%) than men (31/71, 43.7%) in the cases with a parabolic inspiratory FV loop and one inflection point ($p = 0.003$). Conversely, there was a statistically larger percentage of men (27/44, 61.4%) than women (2/27, 7.4%) in the cases with a parabolic inspiratory FV loop and two or more inflection points ($p = 0.003$). The inspiratory FV curve was flattened and smooth in 2 studies (2.0%), flattened and jagged in 1 study (1.0%), and 'other' in 14 studies (14.3%). In those cases where there was disagreement between the authors ($n = 23$), the most common disagreement was whether a parabolic inspiratory curve had one or two inflection points (9 cases).

Table 1. Inspiratory Flow-Volume Data ($n = 121$).

Variable	Number of Cases	%	95% CI
Best FIF_{50}			
≥ 95% MIF on same effort	76	62.8	53.5%–71.3%
≥ 95% on best MIF	70	57.9	48.6%–66.7%
Best MIF plus			
Best FIF_{50} occurred together	103	85.1	77.2%–90.7%
Best FIVC occurred together	58	47.9	38.8%–57.1%
Best (FIVC + FIF_{50} + MIF) effort	111	91.7	84.9%–95.7%
Best FIF_{50} plus			
Best FIVC occurred together	57	47.1	38.0%–56.4%
Best (FIVC + FIF_{50} + MIF) effort	107	88.4	81.0%–93.3%

CI = confidence interval; FIF_{50} = forced inspiratory flow at 50% of vital capacity; MIF = maximum inspiratory flow; FIVC = forced inspiratory vital capacity

Table 2. Forced Inspiratory Vital Capacity (FIVC) and Forced Expiratory Vital Capacity (FVC) Data ($n = 121$).

Variable	Number of Cases	%	95% CI
FIVC on any effort ≥ FVC on same effort	53	43.8	34.5%–53.6%
Best FIVC ≥ FVC on same effort	48	39.7	30.6%–49.5%
Best FIVC ≥ best FVC on any effort	42	34.7	26.0%–44.4%
FIVC ≥ FVC on effort with best MIF	106	87.6	79.6%–92.7%
Best FIVC ≥ 90% FVC on same effort	111	91.7	84.5%–95.9%
Best FIVC ≥ 90% of best FVC on any effort	109	90.1	82.6%–94.7%

MIF = maximum inspiratory flow

Discussion

To our knowledge, the earliest guidelines regarding an acceptable inspiratory FV loop were published by Dillard et al[12] in 1993. These guidelines stated that, "(1) forced inspiratory vital capacity (FIVC) should not be less than 90% of forced expiratory vital capacity (FVC) (2); composite superimposed inspiratory flow-volume curves should be smooth and continuous, without multiple domains of inflection; and (3) inspiratory flow-volume curves should have a parabolic or semicircular shape by inspection without a pronounced plateau."

Table 3. Correlation between Largest Inspiratory Variable Values Based Upon Expiratory Effort on Which They Occurred (n = 121)

Variable	Kendall's Tau-b	Spearman's Correlation
FIF_{50} and (FIVC + FIF_{50} + MIF) on "best effort" expiratory curve	0.840	0.876
FIF_{50} and (FIVC + FIF_{50} + MIF) on 2nd best effort expiratory curve	0.858	0.887
FIF_{50} and (FIVC + FIF_{50} + MIF) on 3rd best effort expiratory curve	0.844	0.864
MIF and FIF_{50} on best effort expiratory curve	0.699	0.748
MIF and FIF_{50} on 2nd best effort expiratory curve	0.739	0.779
MIF and FIF_{50} on 3rd best effort expiratory curve	0.677	0.713
MIF and (FIVC + FIF_{50} + MIF) on best effort expiratory curve	0.823	0.859
MIF and (FIVC + FIF_{50} + MIF) on 2nd best effort expiratory curve	0.853	0.877
MIF and (FIVC + FIF_{50} + MIF) on 3rd best effort expiratory curve	0.807	0.843

All values are statistically significant with $p < 0.001$

FIF_{50} = forced inspiratory flow at 50% of vital capacity, FIVC = forced inspiratory vital capacity, MIF = maximum inspiratory flow rate

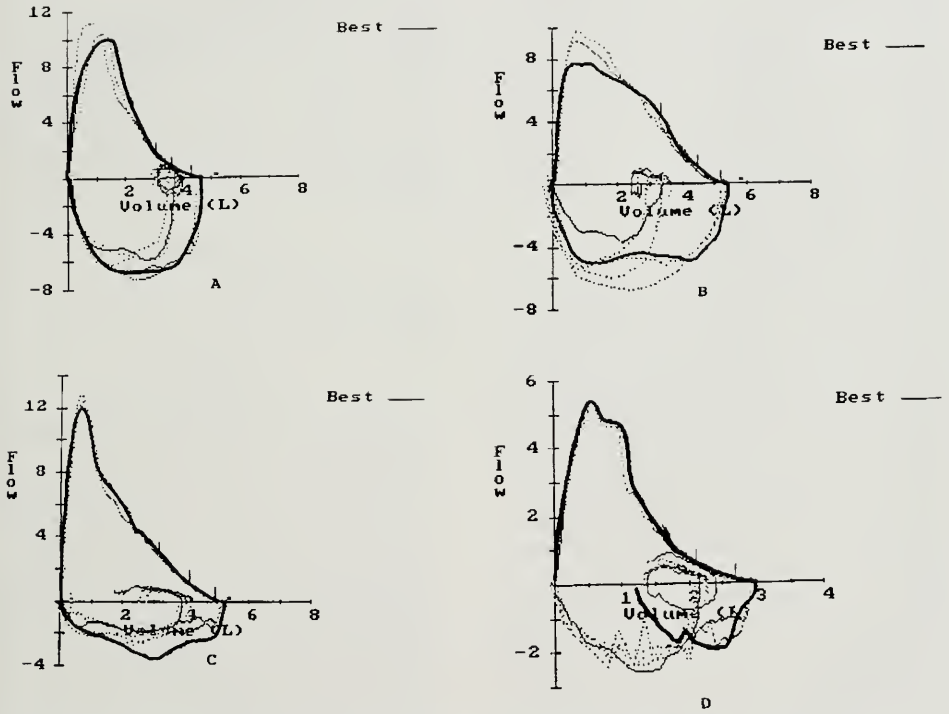

Fig. 1. Representative samples of inspiratory flow-volume curve shapes found during analysis: A, parabolic loop with one inflection point; B, parabolic loop with 2 inflection points; C, flattened, smooth loop; D, 'other' category with jagged, incomplete loop.

In 1994, other guidelines were proposed for "accepting, reporting, and displaying the best inspiratory FV curve data." These included, "(1) The acceptability criteria would require that the FIVC be equal to or greater than the FVC and that the FIF_{50} should be at least 95% of the (MIF). (2) The best data selected for numerical tabulation and ratio determinations should be the largest FIVC, the largest FIF_{50} and the largest (MIF) from all trials. (3) The 'best' inspira-

tory FV curve for printing and interpretation should be chosen as the inspiratory FV curve with the largest sum of the FIVC + FIF_{50} + (MIF) and paired with the best expiratory FV curve."[13]

Our study reveals several important findings. The first is that evaluation of inspiratory FV data obtained from the loop with the best effort expiratory curve misses a significant portion of maximal MIF and FIF_{50} values. Spirometry software, which only displays, saves, and prints the best effort expiratory effort with accompanying inspiratory values, will not provide optimal data for interpretation of the inspiratory FV curve and may lead to FV loop misinterpretations. Second, $FIF_{50} \geq 95\%$ MIF, FIVC $\geq$ FVC, or a curve with parabolic shape and only one inflection point all occur infrequently enough that they are not useful as criteria for an acceptable inspiratory FV curve when the inspiratory FV loop is performed immediately *after* the expiratory maneuver. Third, the largest values for MIF, FIF_{50}, and FIVC do not always occur on the same effort, although the largest FIF_{50} and MIF were usually found on the curve with the largest sum of FIVC + FIF_{50} + MIF. For these variables, examination of all saved trials is necessary to identify the largest values. Last, the FIVC is $\geq 90\%$ FVC frequently enough that it may be useful as a criterion of acceptability. However, FIV_1 and FIVC were not within 5% of their second largest values frequently enough to be useful as criteria of reproducibility.

There are several limitations to our study. The first is that the study was done retrospectively. Although everything possible was done to include normal patients into the study, review of the questionnaire and brief history provided with the requests may not have been enough to exclude everyone with pulmonary disease. Second, the inspiratory loop data were evaluated only from the 3 best saved expiratory efforts. This is a function of the software used in our pulmonary function-testing laboratory. Other software, allowing one to save the best inspiratory efforts and/or perform the inspiratory loop separately from the expiratory effort, may yield different results. It should be noted that there are few programs currently on the market that allow this kind of flexibility. Third, the testing was performed by more than 1 respiratory care provider; however, technicians at our institution are taught to coach every patient all the way through the inspiratory maneuver, until inspiratory effort can no longer be sustained. Last, the evaluation of the shape of the inspiratory FV curve yielded a 19% discordance rate. Until uniform criteria for acceptable shapes of the inspiratory curve are developed, interpretations of shape will always involve some subjectivity.

Despite the limitations of the study, we believe that on the basis of the above findings, it is currently difficult to propose acceptability criteria for a normal inspiratory FV curve that is obtained immediately after the FVC maneuver. The findings of lack of best inspiratory curves following best forced expiratory efforts suggest that additional trials, performed separately from the forced expiratory maneuver, may yield more consistent, best inspiratory curves.

Conclusions

Although the American Thoracic Society provides extensive guidelines for performance of the FVC maneuver, it has not yet adopted guidelines for acceptability of the inspiratory FV curve. We agree with Ewald et al[13] that separate performance of the inspiratory and expiratory maneuvers, with subsequent simultaneous display, is a good starting point, and we repeat their call for the establishment of inspiratory guidelines. On the basis of our findings, when the inspiratory effort is performed immediately following a forced expiratory maneuver, $FIF_{50} \geq 95\%$ MIF, FIVC $\geq$ FVC, or a parabolic shape with only one inflection point are not optimal criteria for a normal or acceptable inspiratory FV curve. However, FIVC $\geq 90\%$ FVC may be useful as a criterion of acceptability. Further evaluation using larger populations is needed before definitive recommendations can be made.

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Ventilatory Management of a Bronchopleural Fistula following Thoracic Surgery

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Bronchopleural fistulae can present a significant therapeutic dilemma in the maintenance of adequate alveolar ventilation. The challenge presented by bronchopleural fistulae relates to keeping airway pressures at or below the critical opening pressure of the fistula in order to promote fistula healing, yet still providing adequate alveolar ventilation for sufficient gas exchange. Occasionally, independent lung ventilation alone or in combination with other less conventional ventilatory strategies is required. We report the case of a patient with a massive bronchopleural fistula following thoracic surgery and present a strategy of management for this challenging clinical problem. [Respir Care 1998;43(12):1064–1069] *Key words: Bronchopleural fistula, ventilation, independent lung ventilation, jet ventilation*

Introduction

Bronchopleural fistulae (BPF) are associated with pulmonary disease, thoracic surgery, trauma, and mechanical ventilation.[1,2] The maintenance of adequate alveolar ventilation despite loss of minute ventilation through the fistula can present a challenging therapeutic dilemma. If the fistula flow is large, hypoxia and hypercarbia may ensue. The essential principle of management centers around maintaining airway pressures below the opening pressure of the fistula in order to minimize the air leak and allow healing. This is not always possible with the use of conventional volume-cycled ventilation. High-frequency jet ventilation (HFJV), which usually produces lower airway pressures than equivalent alveolar ventilation provided by conventional positive pressure ventilation methodologies, can provide a theoretical advantage if adequate ventilation can occur at or below the critical opening pressure of the BPF. This theoretical advantage of HFJV has been shown in animal studies to maintain alveolar ventilation in the presence of a BPF[3–7] but to have no benefit over conventional ventilatory strategies in clinical studies.[8,9] Independent lung ventilation (ILV), used to isolate the BPF, has been shown to be effective treatment of BPF.[10] Crimi et al[11] have described the use of unilateral HFJV in conjunction with ILV in the treatment of BPF.

We present a case of a massive BPF following decortication for acute empyema that healed with unilateral HFJV/ILV. Included is the rationale and the procedures used to establish and later remove HFJV/ILV.

Case Report

The patient was a 75-year-old (85 kg) white man with a history of chronic obstructive pulmonary disease, who presented to an outlying institution with a 1-month history of cough and intermittent fever. The patient was admitted with the diagnosis of community-acquired pneumonia. Shortly after admission, the patient developed respiratory distress, requiring intubation and mechanical ventilation. Despite broad-spectrum antibiotic therapy, the patient's pulmonary dysfunction persisted due to progression of the right lower lobe pneumonia into a parapneumonic empyema. Right thoracotomy and decortication was done; a thick, densely adherent fibrous peel was found. Decortication resulted in loss of much of the visceral pleura and creation of a massive BPF. After the operation, progressively inadequate alveolar ventilation resulted despite the use of ILV with volume-cycled ventilators (Table 1). The patient was transferred to Allegheny University Hospitals

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Table 1. Ventilatory Strategies, Pulmonary Mechanics, Arterial Blood Gases, and Air Leak Assessment.

Time	Ventilator settings: trigger rate (breaths/min); tidal volume (mL) or inspiratory pressure (cm H_2O); F_{IO_2}; CPAP (cm H_2O)	Ventilator Mode	Ventilatory Pattern	Peak Inspiratory Pressure (cm H_2O)	Mean Airway Pressure (cm H_2O)	Air Leak	Arterial Blood Gas (pH, P_{CO_2} [mm Hg], P_{O_2} [mm Hg])
Immediate p-op	(R) A/C-18, V_T-200, .5, +5	VC	Independent	20	NA	7	7.26/59/102
	(L) A/C-18, V_T-350, .5, +5	VC		28	NA		
Transfer	(R) A/C-40, V_T-200, .4, +5	VC	Independent	20	NA	7	7.07/117/66
	(L) A/C-40, V_T-350, .4, +5	VC		43	NA		
HD-1.0	A/C-50, V_T-600, .5, +5	VC	Bilateral	37	21	7	7.11/89/79
HD-1.2	(R) 120, DP-22, Ti-.5,	HFJV		25	13		
	IMV-6, PC-10, .5	PC	Independent			2*	7.37/44/201
	(L) A/C-20, V_T-600, .5, +8	VC		36	23		
HD-6	(R) A/C-12, PC-25, .5, +5	PC	Independent	30	15	0	7.47/40/122
	(L) A/C-12, V_T-600, .5, +10	VC		35	18		
HD-7	A/C-22, PC-35, .5, +12	PC	Bilateral	37	14	0	7.36/53/94

Immediate p-op = status at completion of the decortication; transfer = status at time of transfer to Allegheny University Hospitals MCP on postoperative day 1; HD-1.0 = status at arrival to Allegheny University Hospitals MCP; HD-1.2 = status on hospital day 1, 2 hours after arrival; HD-6 = status on hospital day 6; HD-7 = status on hospital day 7; (R) = right lung; (L) = left lung; A/C = assist/control; IMV = intermittent mandatory ventilation; V_T = tidal volume; F_{IO_2} = fractional inspired oxygen content; CPAP = continuous positive airway pressure; A/C = assist-control; DP = driving (inspiratory) pressure; VC = volume control; PC = pressure control; HFJV = high frequency jet ventilation; NA = not available

* Leak subjectively quantitated using the markings on the air leak meter of the Pleur-evac A-7000

† Leak resolved over 6 days

MCP on the first postoperative day for consideration of alternative ventilatory therapy.

The massive BPF persisted after the patient was transferred (Table 1). A chest radiograph revealed consolidation of the right lung with midline shift toward the diseased side with adequately placed right-sided chest tubes (Fig. 1). The double lumen tube (DLT) that had been placed during the thoracotomy had become malpositioned during transport. Initial management included repositioning the left-sided DLT into optimal position by use of a 4-mm (outer diameter) bronchoscope. Since bilateral ventilation and ILV with conventional ventilatory modes resulted in a persistent massive BPF and inadequate alveolar ventilation, HFJV was instituted on the right side, and a Nellcor Puritan Bennett 7200a was used to supply entrainment gas and ventilatory alarms. On the left side, conventional volume-cycled ventilation was continued.

Over a period of 6 days, the BPF healed, as evidenced by the decrease and eventual cessation of the air leak from the right-sided chest tubes. With resolution of the BPF, plans were made to simplify the ventilatory management. The first step was the removal of HFJV with conversion to ILV using pressure-controlled ventilation (Table 1). The pressure control level on the right side was increased to 28 cm H_2O in an attempt to maintain alveolar recruitment. A trial of bilateral ventilation was accomplished by adapting the DLT connection for one ventilator (Table 1). Since alveolar ventilation was acceptable, the DLT was removed, and airway control was established by tracheostomy. With continued pressure control ventilation, the respiratory acidosis resolved completely.

Over the following week, multiple organ failure ensued. Sputum cultures grew *Pseudomonas aeruginosa*. Computed tomography of the chest revealed two right-sided anterior hydropneumothoraces and gross consolidation of the entire right lung. An anterior chest tube was placed in an attempt to drain these collections. The cardiothoracic surgery department was consulted and did not feel that the patient was an operative candidate. After consultation with the family, it was decided that further aggressive life-support measures should not be undertaken, and despite appropriate antibiotic therapy, the patient expired shortly thereafter.

Discussion

BPF are manifested as simple or tension pneumothoraces or as a continuous air leak from a pre-existing chest tube. The therapeutic predicament involved with BPF is twofold. The first dilemma is the maintenance of adequate alveolar ventilation while ventilatory losses occur through the fistula. In some animal studies,[3] fistula losses contained a large amount of carbon dioxide CO_2, which contributed to the alveolar ventilation and, therefore, did not present a ventilatory problem. Clinically, hypercarbia in the face of a large BPF is a significant problem.[12] The second dilemma relates to closure of the fistula—a physiologic process that may be influenced by the ventilatory

Suppliers of commercial products are identified in the Product Sources section at the end of the text.

Fig. 1. Patient's chest radiograph on transfer to Allegheny University Hospitals MCP, showing consolidation of a large portion of the right lung with midline shift toward the affected side due to volume loss. The arrow shows the position of the bronchial lumen tip of the double lumen endotracheal tube just below the carina at the left main bronchus. Advancement of the tube was necessary due to its cephalad migration. There is a tracheostoma tube in position to maintain patency of the tracheostoma. Nasogastric and nasoduodenal tubes are in place to allow for gastric decompression and enteral feedings, respectively.

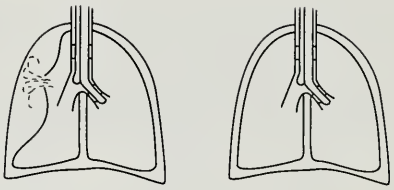

Fig. 2. Flow of air through a bronchopleural fistula depends on the pressure differential between the opening pressure of the fistula and the airway pressure. If the airway pressure is greater than the opening pressure, air will flow through the fistula maintaining its patency; if the airway pressure is less than the fistula opening pressure, there will be no flow through the fistula, thus allowing the potential for healing.

strategy used. Passage of air through the fistula tract is determined by the difference between the airway pressure and a "critical opening pressure" of the BPF (Fig. 2). When airway pressure exceeds this opening pressure, air flows freely through the fistula; however, if the airway pressure remains below the opening pressure, no fistula flow occurs. Theoretically, any positive airway pressure may protract the existence of a BPF. Likewise, any strategy to reduce airway pressure should promote resolution of the BPF; however, in terms of maintenance of alveolar ventilation or time to healing, no prospective, controlled study has been done to show superiority of any ventilatory strategy in the management of BPF. Despite this paucity of scientific evidence, certain principles of management should be followed (Fig. 3).

Regardless of the cause of the BPF, initial management involves insertion of a chest tube attached to a closed suction drainage system. If the loss of minute ventilation through the fistula or increased work of breathing causes ventilatory insufficiency, intubation and mechanical ventilation must be instituted. Positive pressure ventilation can worsen fistula losses secondary to increased airway pressures.

If the fistula is small, a conventional mode of positive pressure ventilation should be used. Volume control ventilation is most commonly used, but airway pressures are not well controlled, and fistula healing may be impaired. Pressure-controlled ventilation may be preferable because peak airway pressures are regulated. Although the efficacy of pressure control over volume control ventilation is unproved, it is our preferred mode of ventilation for BPF management.

If minute ventilation is sufficient to allow an acceptable P_{CO_2}, the patient may be continued on a conventional mode of ventilation; if hypercarbia persists, or if the air leak is large, then the use of HFJV should be considered.

In HFJV (Fig. 4), gas is delivered in short pulses at high pressure through a small-caliber injector.[13] This injection configuration causes entrainment of surrounding gases (the Bernoulli principle); the end result is small tidal volumes at low pressure. If airway pressures are maintained below the critical opening pressure of the BPF, the air leak will decrease, which may promote fistula healing. Low-pressure ventilation may predispose an already poorly compliant lung to further atelectasis. This is especially relevant, as with the present case, in the face of incompletely treated infection. One must balance the desired effect of decreasing airway pressures to minimize the loss of minute ventilation through the BPF against the loss of alveolar units due to collapse as airway pressures decline below critical alveolar closing pressures.

Once ventilation is optimized with HFJV, the amount of gas lost through the BPF should be carefully observed. If the air leak does not decrease over time, or if it is so massive that the acceptable alveolar ventilation cannot be accomplished with HFJV, then ILV is the next recourse. Whole lung HFJV was not done in this case because the DLT was already in position.

Independent lung ventilation can be done with conventional ventilation of the uninvolved lung coupled with either no support, continuous positive airway pressure, pressure- or volume-control ventilation, or HFJV on the side of

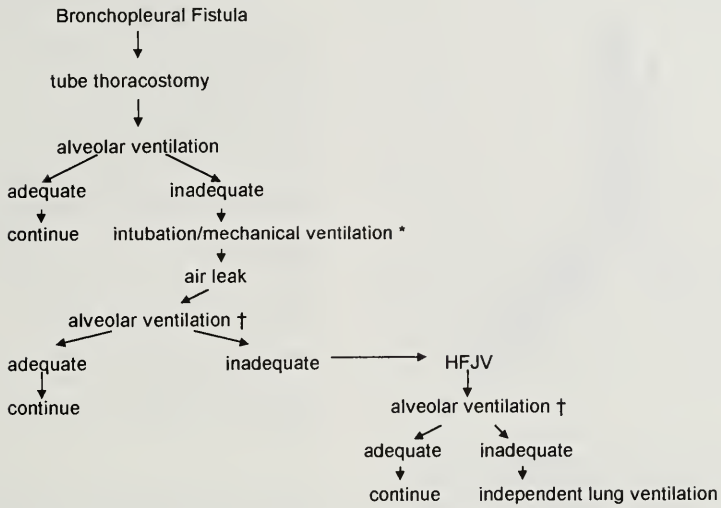

Fig. 3. Proposed management of a bronchopleural fistula. HFJV = high frequency jet ventilation. *Volume or pressure controlled ventilation (see text). †alveolar ventilation that results in an acceptable pH.

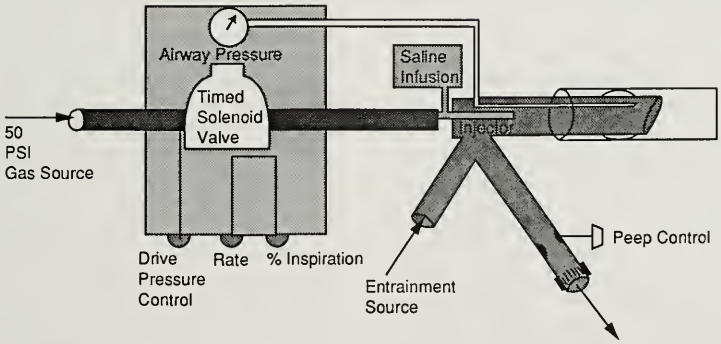

Fig. 4. Schematic representation of the high frequency jet ventilator.

the BPF. The choice of ventilatory support given the lung with the BPF is dependent upon the need for additional alveolar ventilation and the desire to recruit or maintain alveolar units. The predominant problem with ILV is the insertion and stabilization of the DLT (Fig. 5).[14] A left-sided tube is most frequently used because positioning the bronchial lumen of the tube into the longer left main bronchus is less likely to result in obstruction of a segmental bronchial orifice. The position of the DLT must be monitored carefully; malposition can lead to failure. If the tube is too high (with the bronchial lumen in the trachea), the lungs will not be independently ventilated. If the tube is too low (with the bronchial lumen at the distal left main bronchus), the left upper lobe orifice may be obstructed. At extreme distal displacement of the tube (such that the tracheal lumen is in the left main bronchus), the minute ventilation intended for both lungs will be delivered to one lung. This will result in collapse of one lung, with hyperinflation and risk of significant barotrauma or volutrauma of the other. A pediatric bronchoscope, with a maximum outer diameter of 4 mm, should always be used to guide initial placement and subsequent tube position evaluations.

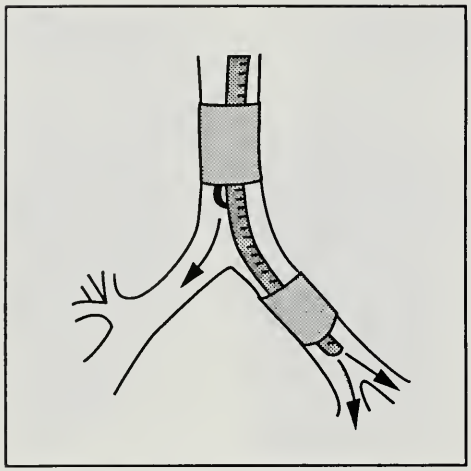

Fig. 5. An artist's rendition of a left-sided Carlen's double lumen endotracheal tube. In this case, the longer bronchial lumen supplies gas to the left lung, while the tracheal lumen just below the carina supplies gas to the right lung. Adequate positioning of this tube can be assessed by auscultation but is best accomplished with the use of a small-caliber bronchoscope (see text). Frequent assessment of tube position is suggested because migration is commonplace with prolonged use.

The margin for acceptable tube position is small, and displacement of a properly placed tube is not infrequent; therefore, frequent radiographs should be used to assure proper tube placement.

When the air leak resolved and the chest radiograph revealed no residual pneumothorax, the BPF was presumed healed. Since ILV with HFJV was used in this case to resolve the BPF, as the first step in simplifying the ventilatory support, we chose the conversion from HFJV to conventional ventilation (Table 2). First, peak and mean airway pressures and lung compliance on both sides should be noted prior to ventilatory changes. Knowledge of the pressures on the diseased side is necessary in order to estimate what pressures the fistula will tolerate without reopening; the contralateral pressures are important because it is these pressures that result in the bulk of the gas exchange, especially with unilateral severe restrictive disease.

If lung compliance is similar in the two lungs, bilateral ventilation can be reestablished with little concern for reopening the BPF as long as the peak and mean pressures are kept at or below the previously tolerated pressures. A trial of bilateral ventilation is best accomplished by adapting the DLT to a single ventilator (adapter supplied with the DLT). If acceptable gas exchange occurs without reopening the BPF, the DLT should be converted to a single

Table 2. Proposed Steps in the Conversion of High Frequency Jet Ventilation-Independent Lung Ventilation to Conventional Bilateral Ventilation

1. Resolve bronchopleural fistula (BPF)
2. Record lung compliance along with peak inspiratory pressure (PIP) and mean airway pressure bilaterally
3. Institute pressure control (PC) ventilation on the side of the BPF at the above PIP, set continuous positive airway pressure to maintain the mean airway pressure at the level of previous HFJV settings; arterial blood gas analysis (ABG)
4. If alveolar recruitment needed, increase PIP by 2 cm H_2O; ABG
5. Once alveolar recruitment is no longer needed, convert double lumen endotracheal tube (DLT) to a functional single lumen with the 2 into 1 circuit adapter supplied with the DLT, set PC ventilation to setting used on the uninvolved side (may result in reduced ventilation to the poorly compliant lung if impedance/resistance is high, leading to alveolar collapse); ABG
6. If ABG is acceptable, change DLT to single lumen tube and wean on intermittent mandatory ventilation with PC ventilation and pressure support ventilation
7. If ABG unacceptable, repeat step 4

lumen tube. We prefer to use pressure control ventilation in the intermittent mechanical ventilation mode with pressure-support ventilation for subsequent mechanical ventilatory support.

If there is a marked discrepancy in compliance, especially if lung consolidation and pneumonia exist, we prefer to maintain ILV using pressure control on the diseased lung in an attempt to "focus" the alveolar recruitment to the noncompliant lung. This attempt at focused recruitment is done to promote lung drainage. Pressure-control ventilation is initiated on the side of the fistula starting at or just below the previously tolerated peak inspiratory pressure, and the continuous positive airway pressure is adjusted to establish the previously tolerated mean pressure. While observing the chest tube for fistula flow, the peak inspiratory pressure is increased in increments of 2 cm H_2O until an acceptable tidal volume is attained. Since disparity in lung compliance may persist for weeks in some disease states, conversion to bilateral ventilation may be delayed or done under less than ideal pulmonary circumstances. In the face of lung compliance disparity, conversion to bilateral ventilation may result in underinflation and worsened consolidation of the diseased lung due to gas flow diversion away from the poorly compliant lung.

Summary

We have reported a case of a BPF that successfully resolved with ILV and HFJV. Therapy of BPF involves healing of the fistula and maintenance of adequate alveolar ventilation during the period of ventilatory loss. A logical strategy for treatment of this difficult clinical problem has been presented.

PRODUCT SOURCES

Double Lumen Endotracheal Tube, Model #39 Carlen's, Rusch Inc, Duluth GA

Bronchoscope (4-mm outer diameter), Olympus America Inc, Melville NY

High Frequency Jet Ventilator, Model VS600, Instrumentation Development Corp, Breathing Services Inc, Ephrata PA

Nellcor Puritan Bennett 7200a, Mallinckrodt Inc, Pleasanton CA

Pleur-evac A-7000 air leak meter, Genzyme Surgical Products, Tucker GA

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Surfactant in Pediatric Respiratory Failure

Douglas F Willson MD

Introduction
Surface Tension and Surfactant
Composition of Surfactant
Surfactant Metabolism
Surfactant in Acute Lung Injury
Surfactant Therapy
Types of Surfactant
Timing of Administration
Method of Delivery
Animal Studies
Human Studies
Future Directions

[Respir Care 1998;43(12):1070–1085] *Key words: Acute hypoxemic respiratory failure, acute respiratory distress syndrome, animal studies, human studies, mechanical ventilation, oxygenation index, physiology, surfactant, therapy.*

Introduction

The successful introduction of surfactant therapy into clinical care is testimony to the value of basic science research. There are few better examples in medicine of how discoveries made in the laboratory can be directly translated into improved clinical care.

The seeds of this advance were sown in the early 19th century with the observations of Pierre Simon de Laplace. In his theory of capillary action LaPlace described the relationship of trans-surface pressure and surface tension at a gas-fluid interface in a sphere:

$$P_{TS} = 2\gamma/r,$$

where P_{TS} is the trans-surface or distending pressure, γ is surface tension, and r is the radius of curvature of the sphere.

More than a century later, von Neergaard[1] applied this concept of a "tension" existing between gas-fluid interfaces to explain his observations on the pressure:volume relationship of the excised dog lung (Fig. 1).[2]. He observed that greater pressure was needed to inflate the lung with air than with a gum arabic-saline solution and hypothesized this was due to the work required to overcome surface tension at the alveolar air-fluid interface predicted by Laplace's theory. Inflation with fluid eliminated this interface and thus required lower pressure.

Twenty years later, Macklin[3] postulated the existence of a continuous "mucoprotein" lining in the lung that had the surface tension–lowering properties observed by von Neergaard. In 1955, Pattle[4] extracted a "waxy substance" from lung washings having such surface tension–lowering properties. Clements[5] subsequently confirmed that Pattle's waxy substance indeed greatly lowered surface tension in vitro when compressed using a modified Wilhelmy balance. It remained for Avery and Mead[6] to demonstrate that this substance was missing from the lungs of preterm infants and Fujiwara et al[7] (along with many others) to produce and successfully use surfactant replacement for preterm babies with infantile respiratory distress syndrome (RDS).

The release of surfactant for clinical use in the United States by the Food and Drug Administration in 1990 resulted in an immediate and measurable reduction in peri-

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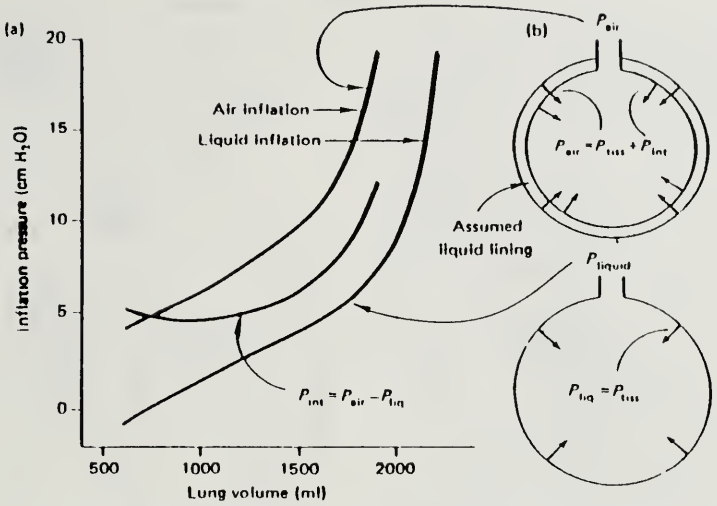

Fig. 1. The original data of von Neergard (1929) are plotted in (a) for liquid-and air-filled lungs, showing how the pressure to inflate with air is appreciably higher than that needed to inflate with fluid. Also depicted is the traditional interpretation by which the difference in recoil has been attributed to a continuous liquid-air interface, ie, to a 'bubble' lining, which would be eliminated by liquid filling as illustrated in (b). (From Reference 2, with permission.)

natal mortality and morbidity.[8] The use of exogenous surfactants for treatment of lung injury beyond the neonatal period is only now being studied but may offer similar promise.

Surface Tension and Surfactant

Surface tension is the consequence of the imbalance in opposing forces at the interface between two phases of matter. Using as an example the interface or "surface" between a liquid and a gas (Fig. 2), the intermolecular forces in the liquid state are stronger than those in the gaseous state. This results in molecules at the liquid surface being disproportionately pulled back into the fluid, creating a pressure or tension at the surface that resists disruption. Pulling surface molecules out of the liquid requires more energy than moving subsurface molecules through the liquid. It is this tension, for example, that allows a steel needle to float on the surface of the water despite the needle's greater density. In a spherical construct, such as a bubble, these surface interactions increase as the bubble gets smaller (in accordance with Laplace's law) and cause it to collapse upon itself.

Surfactants are substances capable of modifying the surface tension between interfaces. In biologic systems, this primarily means interfaces involving air and aqueous solutions. Most biologic surfactants are amphipathic molecules—that is, molecules with combinations of hydrophilic (water loving) and hydrophobic (water hating) functional groups or moieties. Amphipathic molecules adsorbed at an aqueous interface orient with the hydrophilic moiety aligned to the aqueous phase and the hydrophobic moiety aligned to the nonaqueous phase—in effect creating a new interface. This new interface has less "surface energy" or "tension" because the attraction of the hydrophilic moiety to the aqueous phase is balanced by the repulsion of the hydrophobic moiety. Amphipathic molecules thus act as

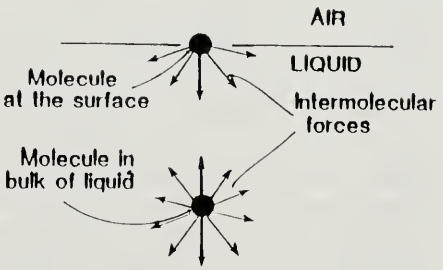

Fig. 2. Depicting the sphere of intermolecular forces for a molecule in the bulk of liquid and how this becomes a hemisphere with a net force of attraction toward the bulk of the liquid when that molecule is relocated at the surface. (From Reference 9, with permission.)

bridges or transitions, substituting their high internal chemical bond energy (from the close internal proximity of hydrophilic and hydrophobic moieties) for surface energy.

In addition to their surface tension–lowering properties, surfactants spontaneously form surface films at gas-fluid interfaces, a process known as adsorption. For example, the phospholipid mixtures found in most biologic surfactants will rapidly form a monomolecular film at an air-water interface, with the polar hydrophilic phospholipid head groups oriented to the fluid surface and the hydrophobic fatty acid "tails" extending into the air. Both the speed and degree of adsorption (or spreading) are inherent properties of the surfactant.

Although not an entirely accurate description, the lung can be thought of as a (very) large number of interconnected "bubbles." These bubbles form the interface between the gaseous environment and the wet alveolar surface. If this interface were solely between air and water (ie, without surfactant), then three consequences would ensue: (1) It would take, at each breath, considerable distending pressure (comparable to the estimated 80–90 cm H_2O pressure required with a baby's first breath) to expand the lung; (2) the lung would rapidly collapse during exhalation; (3) alveolar size in the lung would need to be fairly uniform or alveoli with large radii would tend to be better ventilated than smaller alveoli, and smaller alveoli would tend to empty into larger ones. Indeed it was the deviation from these expected behaviors that suggested the existence of surface-active substances in the lung.

Pulmonary surfactant functions to lower surface tension at all lung volumes, but of more importance, it decreases surface tension as alveolar surface decreases. As illustrated in Fig. 3,[10] surface tension at a water-surfactant-air interface approaches zero at low relative area (the film is compressed) and increases with expansion of the film. Decreased surface tension with compression is due to tighter packing of phospholipids and the resultant exclusion of water molecules from the surface layer. If surface tension did not decrease with compression of the surfactant, alveoli of different size would require different distending pressures (Laplace's Law, $\Delta P = 2\gamma/r$, where γ is surface tension and r is the radius). Small alveoli would empty into large ones, and there would be an increasing propensity for the lung to either collapse or coalesce into a smaller number of large "bubbles" as lung volume diminished. In summary, it is not only that surfactant decreases surface tension but that it reduces it to a greater degree at low lung volume and, thus, counteracts the effect of decreasing alveolar size.

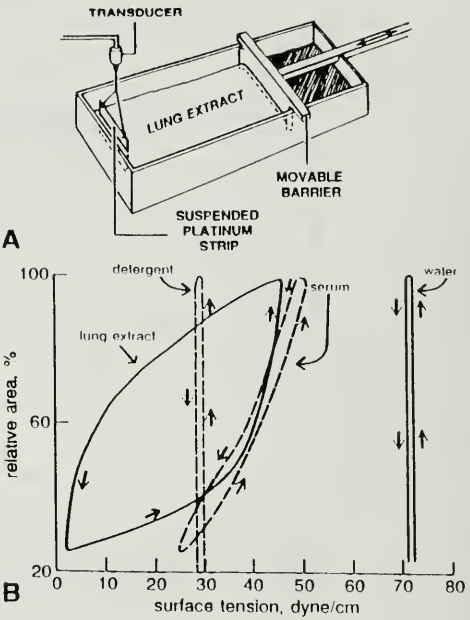

Fig. 3A. Langmuir-Wilhelmy balance for the measurements of surface tension. Liquid containing a surface-active agent is placed in the trough. Surface tension, measured as the force on the platinum strip suspended from a transducer, is continuously recorded as the movable barrier changes the surface area of the air-liquid interface. B. Surface tension–area relationships of water, water with detergent, serum, and alveolar washings obtained in a Langmuir-Wilhelmy balance. The lung washings show a change in surface tension with area, with different values of surface tensions obtained during compression and expansion (hysteresis). Minimum surface tension is close to zero. The surface tension–area relationship of washings from a surfactant-deficient lung resemble that of serum (small hysteresis and high minimum surface tension). (From Reference 10, with permission.)

Composition of Surfactant

Natural surfactant is a complex mixture of phospholipids, neutral lipids, and protein (Table 1).[11] Phospholipids constitute the major component (80% by weight), with the majority consisting of phosphatidylcholine (saturated and unsaturated). The phospholipid components in surfactant are not unique; they are found in most biologic membranes. Neutral lipids make up ~ 10% (mostly cholesterol), and proteins constitutes the remainder. It is likely that each of the components—as well as the balance of components—is important in adsorption, film formation, and the behavior of the film at the alveolar surface. Synthetic mixtures of phospholipids alone (eg, Exosurf,* ALEC)

*Suppliers of commercial products are identified in the Product Sources section at the end of the text.

Table 1. Composition of Pulmonary Surfactant.*

Component	%
Lipid	90–95
Phospholipid	78
Saturated phosphatidylcholine	45
Unsaturated phosphatidylcholine	20
Phosphatidylglycerol	8
Other phospholipids	5
Neutral lipids	10
Other lipids	2
Protein†	5–10
Loosely associated, mainly serum‡	0–5
Apoproteins	5–10

*Values are the approximate percentage masses of individual components in surfactant isolated from alveolar washings by sedimentation and density gradient centrifugation. This material contains many different surfactant structures, including lamellar body contents, tubular myelin, and variably sized vesicles. The composition of each structure may differ from the average composition presented.
†The protein content varies as a function of the purification procedure used. Serum proteins are the major loosely associated protein group, but several lung-specific proteins that have no known role in surfactant function also have been identified in surfactant preparations.
From reference 11, with permission.

Table 2. Surfactant Apoproteins.

Name	Prepro-protein (kDa)*	Post-translational modifications	Protein (kDa)†	Possible functions
SP-A	28,000	Signal peptide cleavage Glycosylation Hydroxylation Acetylation Sulfation Oligomerization	28,000–38,000	Tubular myelin formation Adsorption Secretion Recycling Macrophage phagocytosis
SP-D	40,000	Signal peptide cleavage Glycosylation Oligomerization	42,000	Pathogen agglutination Viral infectivity
SP-B	43,000	Signal peptide cleavage Glycosylation Proteolytic processing	9000	Tubular myelin formation Adsorption
SP-C	21,000	Proteolytic cleavage	4000	Adsorption

SP = surfactant-associated protein.
*Molecular weight of primary translation product predicted from cDNA sequence.
†Molecular weight determined by polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate and disulfide-reducing agents.
From reference 12, with permission.

may have similar surface tension–lowering activities in vitro but are less effective than natural surfactants in vivo, probably because of differences in adsorption and film formation.

The protein content of pharmacologic surfactant preparations is variable and determined largely by the extraction process used. Four surfactant proteins have been identified, usually referred to as surfactant-associated proteins A, B, C, and D (SP-A, -B, -C, and -D) (Table 2).[12] SP-A is a large, collagen-like glycoprotein with a molecular weight of 26,000–36,000 kDa and is the most abundant of the surfactant-associated proteins.[13–15] It forms large oligomers that are remarkably similar to C1q, a subunit of the first component of complement. Because the molecule is hydrophilic, it is excluded in the extraction process of currently available "natural" surfactants. SP-A is thought to be important in the regulation of surfactant metabolism and in the formation of tubular myelin (see below in this section).[16] Its complement-like structure suggests it may also play a role in immune function.[17]

Another hydrophilic surfactant-associated protein, SP-D, has been recently identified. As with SP-A, it is a collagen-like protein that forms large oligomers. The role of SP-D is unclear.[18]

The other two surfactant-associated proteins, SP-B and SP-C, are hydrophobic molecules and extract with the phospholipids in natural surfactants. These are both relatively small proteins that are present in approximately equal amounts (1%–2% of surfactant by weight). Both are thought to play a major role in adsorption of surfactant, and SP-B may also participate in tubular myelin formation.[19] The presence of SP-B and SP-C is likely the primary reason for the greater efficacy of natural relative to synthetic surfactants.

Surfactant Metabolism

The metabolism of surfactant is complex and incompletely understood (Fig. 4).[20] Surfactant is synthesized solely in the type II alveolar pneumocyte. The phospholipid components are synthesized in the endoplasmic reticulum and transported through the Golgi apparatus to the lamellar bodies.[21] Surfactant-associated proteins are translated in the usual fashion but then undergo extensive post-translational processing. SP-A is highly glycosylated and at some point after glycosylation forms large oligomers before joining the phospholipid components in the lamellar bodies.[22] Both SP-B and SP-C are synthesized as pre-pro-proteins and undergo posttranslational cleavage.[23] Both are found in lamellar bodies.

The lamellar bodies are subcellular organelles that are secreted from type II alveolar cells. They are composed of tightly packed membrane-like structures, the composition of which is identical to the surfactant isolated from the alveolar space. The core of the lamellar bodies contains electron-dense material that appears to be protein.[24,25] Lamellar bodies make their way to the cell surface and are

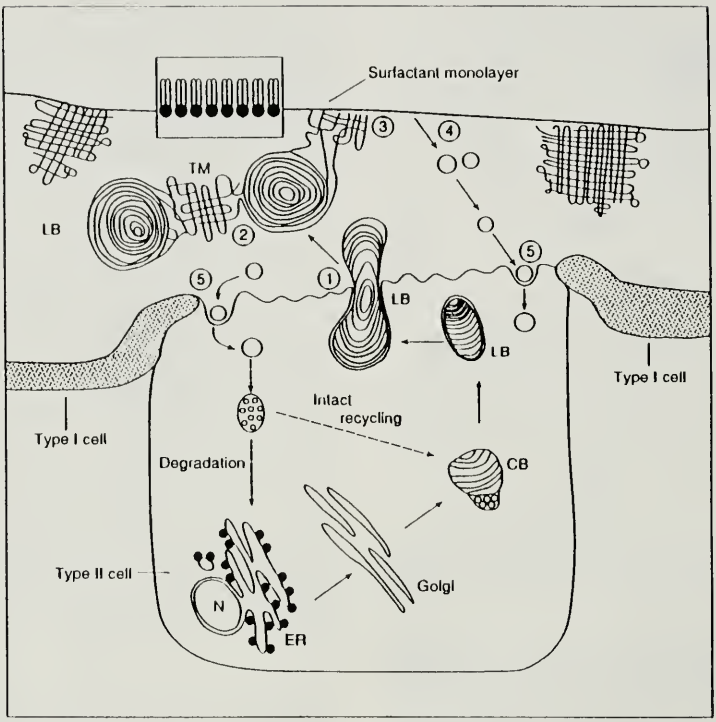

Fig. 4. Schematic diagram of surfactant metabolism. Generally accepted pathways are indicated by solid arrows. Less well-substantiated pathways are indicated by broken arrows. N = nucleus; ER = endoplasmic reticulum; CB = composite body; LB = lamellar body; TM = tubular myelin; 1 = secretion of LB; 2 = conversion of LB into TM; 3 = generation of monolayer from TM material; 4 = formation of small aggregate material from monolayer; 5 = reuptake of surfactant material. (From Reference 20, with permission.)

extruded to seemingly unwind over the alveolar surface into a lattice-like construction called tubular myelin.[26] During this process, the tubular myelin becomes studded with regularly spaced particles, which are thought to be SP-A.[27] The next step involving adsorption of phospholipid from this tubular myelin structure onto the alveolar surface film is not understood, but the alveolar surface film is composed of nearly pure dipalmitoylphosphatidylcholine (DPPC).[28]

The half-time for turnover of human alveolar surfactant is not known, but in animals, such as rats and rabbits, it is 5–10 hours.[29] Secretion and clearance are balanced, with 90% of the surfactant being recycled by the type II pneumocyte. Studies using labeled surfactant introduced into the airways showed that the majority are taken up directly by the pneumocyte, repackaged in lamellar bodies, and eventually re-secreted.[30] Alveolar macrophages are responsible for the remaining 10% of clearance.[31] Several factors, including hyperventilation,[32] β agonists,[33] corticosteroids,[34] leukotrienes,[35] prostaglandins,[35] and adenosine,[35] increase surfactant secretion and clearance, but direct and indirect evidence suggests that SP-A is a primary regulator of surfactant metabolism.[36,37]

Surfactant in Acute Lung Injury

Ashbaugh et al[38] and Petty and colleagues[39,40] in their original descriptions of (acute) adult RDS (acute respiratory distress syndrome [ARDS]) commented on its similarity with infantile RDS and speculated that injury to the surfactant system might be responsible. Given the importance of surfactant in normal pulmonary function, it is tempting to place surfactant dysfunction at the core of

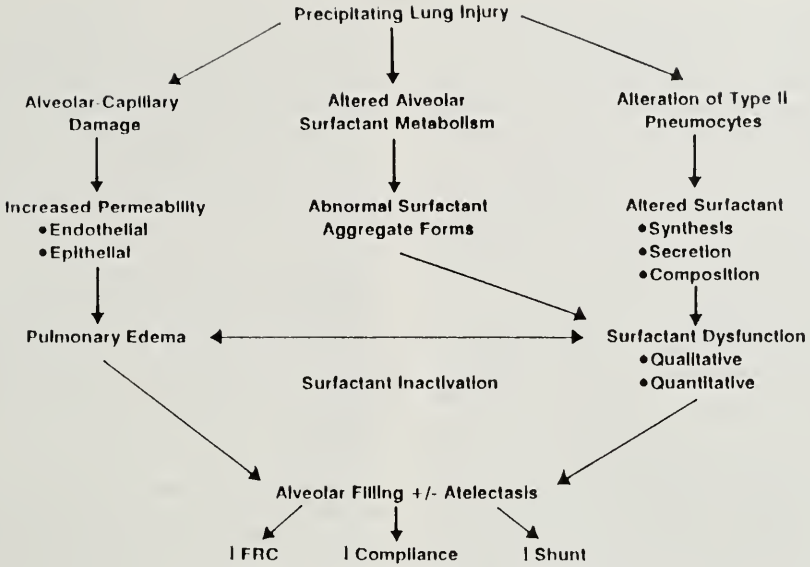

Fig. 5. Flow diagram summarizing the role of altered endogenous surfactant in the pathogenesis of acute respiratory distress syndrome. Included are various mechanisms contributing to altered surfactant function. (From Reference 41, with permission.)

many types of acute lung injury (Fig. 5).[41] However, while the central role of surfactant dysfunction in infantile RDS is well established, the evidence in other causes of respiratory failure is more tenuous. Nonetheless, irregularities in surfactant pool size, changes in composition and metabolism, and inactivation of surfactant have all been described in ARDS and other types of acute lung injury.

Evidence for altered surfactant pool size in acute lung injury is inconsistent: decreased,[42–44] unchanged,[45,46] and increased[47,48] pool size have all been reported. The confusion undoubtedly reflects the difficulty in quantitation of material obtained from bronchoalveolar lavage, the standard methodology used to make these estimates. Phospholipid recovery needs to be standardized to markers of alveolar fluid volume, but no ideal standard has been identified. It is also likely that different injuries may have quite different effects. For example, prolonged exposure of rabbits to 85% oxygen results in type II alveolar cell hyperplasia and increased surfactant secretion,[47] whereas 100% exposure decreases alveolar cell number and surfactant secretion.[49] At present, no firm conclusions regarding the effects of acute lung injury on surfactant pool size can be drawn.

Alteration in the composition of surfactant, however, has been a consistent finding in both animal and human studies of acute lung injury. Decreased surfactant-associated proteins for patients with ARDS and at high risk for ARDS have been described.[43] A consistent finding is decreased relative quantities of saturated phosphatidylcholine and phosphatidylglycerol in conjunction with increased phosphatidylinositol, sphingomyelin, and lysophosphatidylcholine.[50] Furthermore, these abnormalities reverse with recovery from acute lung injury.[41] The relationship of these abnormalities in surfactant composition to lung dysfunction is not known, although several studies have shown that surfactant isolated from animal lung injury models has abnormal surface activity.[51–53]

Several lines of evidence provide support that surfactant metabolism may be altered in acute lung injury. Animals injured with hyperoxia have decreased incorporation of surfactant precursors into lung tissue that reverses with recovery.[54,55] Several animal models of lung injury have shown more rapid conversion of large surfactant aggregate to small surfactant aggregate forms—a form that has very poor surface tension–lowering properties.[56,57] Human bronchoscopic alveolar lavage specimens from patients with ARDS have shown increased levels of proteases and alterations in the density profiles of surfactant.[58]

The most consistent surfactant abnormality seen in acute lung injury has been inactivation by protein. Albumin,

hemoglobin, fibrin, complement, and other proteins that may gain access to the alveolar space secondary to injury to the alveolar-capillary membrane can be shown in vitro to diminish surfactant's surface tension–reducing properties.[59–62] Proteins compete with surfactant for the air-fluid interface and interfere with monolayer formation. In this way, regardless of the initiating event, permeability pulmonary edema can result in surfactant inactivation and in the diminished lung compliance, increased intrapulmonary shunting, and atelectasis characteristic of ARDS (see Fig. 5).[63] Of interest, the surfactant appears to be unaltered, as it can be shown to have normal activity when separated from the protein by simple centrifugation.

Other factors may also be involved in surfactant dysfunction. Oxygen-free radicals,[64,65] cytokines,[66] phospholipases, and proteases[67,68] released by activated leukocytes may inactivate surfactant directly. It is also likely that direct injury to type II alveolar cells may lead to decreased surfactant synthesis and secretion. Loss or injury to these cells may also impact the reuptake and clearance of small aggregate surfactant, leading to loss of surfactant precursors.

In summary, there is ample evidence of surfactant dysfunction in many causes of acute lung injury. The degree of dysfunction may actually correlate with the severity of respiratory failure, as shown by Pison et al[46] in trauma patients. How much surfactant dysfunction contributes to ultimate morbidity and mortality is less clear and is likely dependent on the particular type and degree of lung insult. Furthermore, it is important to realize that pulmonary injury is not a static phenomenon. For example, the initial injury to the capillary-alveolar membrane in ARDS evolves from an exudative phase to intense inflammation, ending in a proliferative and fibrotic stage. The superimposition of barotrauma from ventilatory support further confounds the pathology. The role surfactant dysfunction plays is almost certainly dependent on the stage of the disease in question. While academic, these issues are important to consider when evaluating the potential efficacy of exogenous surfactant as a therapy.

Surfactant Therapy

Even if surfactant dysfunction is at the core of the disturbed physiology, it does not necessarily follow that surfactant administration will be a panacea or even salutary in acute lung injury. Data from animal studies and preterm infants are encouraging, but there have been very few studies in adults or children beyond the neonatal period. What follows is primarily gleaned from these sources and from the few non-neonatal studies published to date; however, more work needs to be done before firm conclusions can be drawn.

Types of Surfactant

Surfactant composition is very similar for all mammalian species. Four different types of exogenous surfactants have been studied in animal and human trials:[69] natural, modified natural, artificial, and synthetic natural surfactants.

Natural surfactants are those that are recovered from lung or amniotic fluid, contain large surfactant aggregates, and have excellent surface-active properties. Unfortunately, they are also difficult to manufacture and carry an infection risk.

Modified natural surfactants are sterile lipid extracts of minced lung or alveolar lavage that have been modified by the addition or removal of compounds. In the lipid-extraction process, the hydrophilic surfactant-associated proteins A and D are excluded, but the hydrophobic surfactant-associated proteins B and C are not. Modified natural surfactants generally have excellent surface activity both in vitro and in vivo.

Artificial surfactants are simply mixtures of synthetic compounds that may or may not resemble the lipid composition of natural surfactant. These compounds behave similarly to natural surfactants in vitro but tend to be less effective in vivo, perhaps because of differences in adsorption at the air-fluid interface; however, they are inexpensive and carry no infection risk.

Synthetic natural surfactants are artificial surfactants with genetically engineered surfactant-associated proteins added. These are not currently available but are likely to be in the future, as the genes for the surfactant associated proteins have been identified and cloned.[70,71]

The various surfactant preparations that have been subjected to clinical trials have been reviewed elsewhere.[72] Currently, only three surfactant preparations have been approved for clinical use in the United States: Survanta, Exosurf, and Infasurf. Survanta is made from minced bovine lung, to which is added DPPC, tripalmitin, and palmitic acid. Exosurf is a synthetic mixture of DPPC with hexadecanol and tyloxapol added to improve adsorption. Infasurf is an unmodified lipid extract of calf lung washings.

Subtle differences in surfactant composition may be important in efficacy. The modified natural surfactants have been shown to be superior to artificial surfactants at improving oxygenation, decreasing mortality, and lowering the incidence of retinopathy and bronchopulmonary dysplasia (BPD) in human neonates.[73–82] Studies in animals suggest that natural surfactants resist inactivation by protein and spread more rapidly at the alveolar surface.[83,84] Comparison of two different natural surfactants in lambs, beractant (Survanta) and CLSE (Infasurf), have shown differences in duration of improvement in oxygenation and lung compliance.[85,86] Thus all surfactants are not equivalent, and efficacy may be somewhat dependent on the formulation used.

Timing of Administration

Diminished lung compliance is one of the early hallmarks of ARDS and is associated with surfactant dysfunction.[44,46,50] Diminished lung compliance may necessitate increased ventilator pressures or volumes (or both) to maintain oxygenation and ventilation that can, in turn, lead to further lung injury. Even relatively short periods of high-pressure ventilation can lead to capillary fracture and increased transmural protein flux into the alveolus.[87–89] Surfactant replacement therapy changes lung volumes, compliance, gas exchange, and time constants toward those of normal lungs and may thus allow avoidance of ventilator-induced lung injury. In preterm animal models, early surfactant replacement before ventilation is established prevents the development of bronchiolar epithelial injury and subsequent lung damage.[90,91] Similarly, studies in preterm human infants at high risk for development of RDS have shown that early (prophylactic) treatment is superior to treatment given once RDS has developed.[92,93] This may be related to avoidance of ventilator-induced lung injury due to improved lung compliance with surfactant administration and to more uniform distribution of surfactant when it is administered before significant ventilator-induced lung injury occurs.

The pathophysiology of ARDS is complex, but there is increasing evidence that the high ventilator pressures and volumes often needed for support may exacerbate existing lung injury. The lung becomes increasingly heterogeneous, with a large proportion of alveoli atelectatic or filled with fluid, leaving oxygenation and ventilation to be accomplished by a markedly reduced proportion of lung.[94] If such injury is related to duration and degree of exposure to high ventilator pressures or volumes (or both), it is reasonable to assert that early treatment—as in infantile RDS—is likely to meet with greater success than later treatment. It is also likely that distribution of surfactant will be more uniform the earlier in the course of lung injury it is given. While these assertions are not proven, it makes intuitive sense that early treatment with surfactant would have the greatest chance for success. The timing of surfactant administration has not been addressed in the few studies of surfactant therapy beyond the neonatal period. This may partially explain the inconsistent results.

Method of Delivery

The method of delivery of surfactant is also important. The two approaches that have been taken are direct bolus instillation down the endotracheal tube and prolonged aerosolization via inspired gas. In clinical practice, bolus instillation has been the approach adopted for neonates (turning the baby during administration to allow gravity to aid in the distribution). In larger children and adults, this entails using large volumes of surfactant (80 mL/m^2 in our trial) and is somewhat labor intensive (particularly for larger patients!). An additional problem is that the potential transient airway obstruction from the bolus can further destabilize the patient. Large volumes of surfactant are also expensive. In contrast, aerosolization requires much smaller volumes of surfactant, is less labor intensive, and does not acutely change ventilation. In a uniform lung-injury model in rabbits (repeated saline lavage), Lewis et al[95] reported that aerosolized beractant (Survanta) resulted in greater improvement in oxygenation and compliance than did instilled beractant despite a much smaller total dose. However, in studies with nonuniform lung injury, aerosolization resulted in preferential distribution to already ventilated lung units, with little to none of the surfactant reaching nonventilated areas and no improvement in oxygenation.[96,97]

No comparative clinical trial of instillation versus aerosolization has been published. The only reported trial of aerosolized surfactant showed no efficacy of aerosolized Exosurf in adults with ARDS.[98] Whether this failure was due to the method of delivery, the surfactant used, or simple lack of efficacy of surfactant in ARDS is unclear. In the absence of further data, in our own clinical trials of surfactant therapy in children with acute hypoxemic respiratory failure,[99,100] we chose instillation, modeling our technique on that utilized in most neonatal studies. Children were given four equal aliquots administered in each of four positions: left side down, head up; left side down, head down; right side down, head up; and right side down, head down. While this approach was cumbersome, it was generally well tolerated. In larger patients, direct instillation into each lobe, using a bronchoscope, has been reported.[101]

The ideal dose and method of surfactant delivery are unclear but represent significant issues because of cost and relative untoward effects. It is possible that some combination of bolus administration followed by aerosolization could be the ideal approach.

Animal Studies

Animal studies have demonstrated that the effect of exogenous surfactant replacement is determined by the lung-injury model used, the timing of the intervention, the dose and composition of the surfactant utilized, and probably other factors not yet understood. As these studies formed the basis for the introduction of surfactant into clinical care, they have been and will continue to be important to our understanding of when and in which patients exogenous surfactant is likely to be effective.

The most commonly used animal lung-injury model is lung lavage. Repeated lavage with warm saline results in surfactant washout and a subsequent inflammatory re-

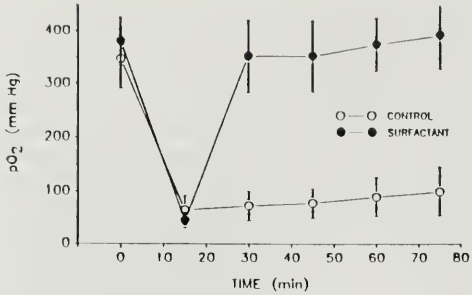

Fig. 6. Response of lavaged guinea pigs to treatment with surfactant. Following repeated lavages, the partial pressure of oxygen (P_{O_2}) values decreased from > 300 mm Hg to < 100 mm Hg despite ventilation with 100% O_2. The animals were then treated at 15 min with a natural pig lung surfactant that resulted in the P_{O_2} values returning to prelavage values. (From Reference 102, with permission.)

sponse. The clinical appearance is quite comparable to infantile RDS, with loss of lung volume, decreased lung compliance, hypoxia, and severe respiratory distress. This model has the advantages of being easily reproducible and not immediately lethal, and it can be produced in a variety of large and small animals. Early surfactant replacement in this injury model (Fig. 6) effectively reverses the clinical signs and symptoms of respiratory distress, just as it does in preterm infants with surfactant deficiency. The model has been fairly well standardized and has been used to compare different types of surfactant and methods of delivery.

Hyperoxic lung injury has been extensively studied by Holm and colleagues[39,55] and Matalon and Egan.[103,104] Rabbits exposed to 100% oxygen for 64 hours develop increased alveolar permeability to protein and decreased surfactant synthesis in alveolar type II cells. Bronchoalveolar lavage reveals markedly diminished phospholipid levels and surfactant with severely impaired dynamic surface activity. Many of the rabbits go on to die of hypoxic respiratory failure. These changes are similar to those described in patients dying of ARDS and can be ameliorated by treatment with exogenous surfactant.[105] Surfactant-treated animals after hyperoxic injury have improved lung mechanics, less severe hypoxia, and reduced mortality.

Other models of lung injury in which surfactant has been investigated include oleic acid injection,[106,107] N-nitroso-N-methylurethane (NNNMU) instillation,[108,109] hydrochloric acid instillation,[110] smoke inhalation,[111] viral infection,[112] and bilateral cervical vagotomy.[113] Oleic acid injection produces an abrupt and severe hemorrhagic pulmonary edema, which does not appear to respond to surfactant.[114] N-nitroso-N-methylurethane produces a more subacute lung injury, with worsening respiratory function over 2–4 days, for which large doses of surfactant appear helpful but not curative.[115] Similarly, treatment with exogenous surfactant is somewhat effective in animal models of hydrochloric acid, smoke inhalation, viral infection, and bilateral vagotomy. In these models, the primary effect of exogenous surfactant is most likely reversal of the endogenous surfactant inhibition by protein that has leaked into the alveolar space after alveolar-capillary endothelial injury. Several of these models have also shown improved response to exogenous surfactant with prior lung lavage, further supporting the role played by protein or other inhibiting substances in the alveolar space.

In summary, exogenous surfactant has shown efficacy in a variety of animal models of lung injury. Exogenous surfactant may replace surfactant that is deficient from loss or inadequate synthesis or it may serve as a source of precursors as it is broken down and taken back up into the type II pneumocytes. Larger doses may overcome the inhibition of protein on the surface lining through sheer competition for the air-fluid interface.

Human Studies

Most of the well-conducted human clinical studies and the bulk of the clinical experience with surfactant is in neonates. Fujiwara et al[7] reported the first clinical trial of rescue therapy for neonates with RDS in 1980. Since then, more than 40 randomized, controlled clinical trials of RDS have been reported, and the results have been remarkably positive. A meta-analysis of the results of 35 clinical trials was performed by Jobe[116] (Fig. 7). This meta-analysis and subsequent clinical trials since 1992 have borne out that surfactant delivered by instillation decreases both morbidity and mortality in infants with RDS. Surfactant therapy has led to a demonstrable decrease in infant mortality in the United States during the last decade.[8] Differences in morbidity are less impressive, with no significant difference in the incidence of BPD or intraventricular hemorrhage but significant decreases in air leaks. The BPD statistic is somewhat misleading, however, as more fragile infants are surviving to develop chronic lung disease, and the incidence would likely be significantly less if these infants were excluded. Comparative trials show natural surfactants to be more effective than synthetic surfactants,[73–82,117] and prophylactic treatment appears better than rescue treatment for those infants at highest risk (neonates from 29–32 weeks gestation).[92,93] Treatment regimens have varied somewhat, but most protocols have used multiple doses, usually scheduled 6–12 hours apart, beginning either in the delivery room or at the first clinical sign of respiratory distress. The dose used is extrapolated to completely replace the normal surfactant pool (100 mg/kg of phospholipid, 80 mL/m^2 or ~ 3 cc/kg) and is delivered in four equal aliquots in four different positions, making use

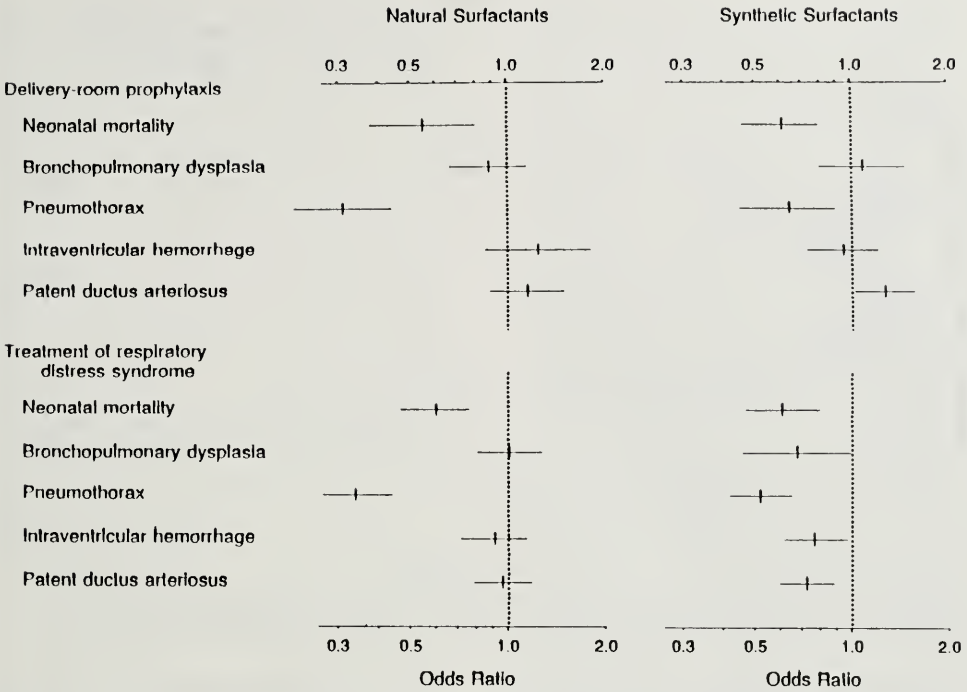

Fig. 7. Odds Ratios from 4 meta-analyses of clinical trials of the effects of surfactant odds ratios and 95% confidence interval from the meta-analyses[125–128] are shown. The meta-analyses were of 8 trials (involving 930 infants) of natural surfactant administered in the delivery room,[129–135] 12 trials (1451 infants) of natural surfactant for the treatment of respiratory distress syndrome (RDS),[136–147] 7 trials (1492 infants) of synthetic surfactant administered in the delivery room,[148–154] and 5 trials (2126 infants) of synthetic surfactant for the treatment of RDS.[152,153,155–157] Neonatal mortality was defined as death from any cause before the 29th day of life, and intraventricular hemorrhage as severe hemorrhage categorized as grade III (extensive intraventricular hemorrhage with ventricular enlargement) or grade IV (intraparenchymal hemorrhage). (From Reference 116, with permission.)

of gravity to distribute the substance to all parts of the lung. Surfactant has been the most studied drug ever introduced into neonatal care, and its use has now become the standard of care in the United States for preterm neonates with or at risk for RDS.

Beyond the neonatal age, the efficacy of exogenous surfactant in respiratory failure has been suggested by several small uncontrolled pilot studies and case reports,[118–123] but the results of the few controlled studies have been mixed. The aerosolized surfactant (Exosurf) study[98] evaluated Exosurf in adults with sepsis-induced ARDS who received nebulized Exosurf continuously for 5 days: They had no improvement in immediate physiology or long-term outcome. This failure may relate to using a synthetic rather than natural surfactant or to aerosolizing the surfactant rather than instilling it. Aerosolized artificial surfactants have proven ineffective in treatment of neonatal RDS,[124,125] and animal studies have shown that aerosolization results in both limited delivery and poor distribution.[95–97] Another study, by Gregory, et al,[122] evaluated the effectiveness of multiple doses of a modified natural surfactant (Survanta) in adults with ARDS. The study demonstrated improvement in oxygenation only in the subgroup receiving four doses (at 100 mg/kg) of surfactant. There was a trend toward lower mortality in the 2 groups receiving the larger doses (100 mg/kg) of surfactant, but differences were not significant when controls were compared with the treated patients. Although promising, the results of this study are confounded by inconsistencies in dosing strategy and randomization and in timing of surfactant administration. Our own prospective controlled trial of calf lung surfactant extract (Infasurf) in children with hypoxemic respiratory failure showed an immediate and striking improvement in oxygenation when administered

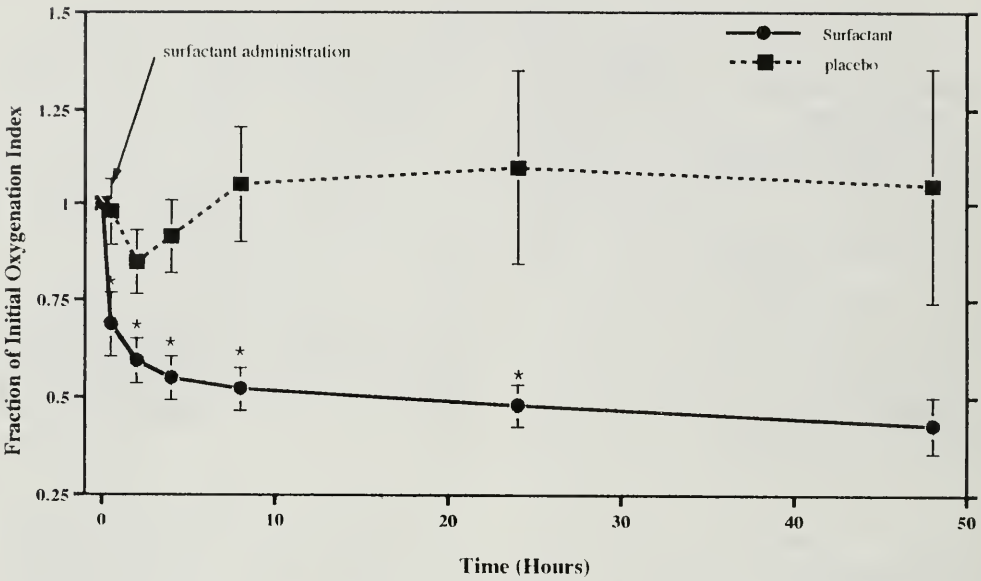

Fig. 8. Changes in oxygenation index in the 48 hours immediately after administration of calf lung surfactant extract. Surfactant is administered at time 0. Solid line = treated patients, dotted line = placebo. * p [lt] 0.05. (From Reference 99, with permission.)

early in respiratory failure (Fig. 8) but no difference in mortality.[100] However, the mortality for both groups was low (11%), and only 1 of 5 deaths was due to respiratory failure. A 32% decrease in the time on mechanical ventilation and a 30% reduction in the intensive care unit stay was demonstrated (Table 3). The discrepancy in efficacy demonstrated by these two studies may relate to differences in patient populations, differences in surfactant formulation, or differences in timing of administration.

Surfactant administration appears to be safe. While bolus administration can be associated with transient hypoxemia and hemodynamic instability, allergic or other immune-mediated responses have not been reported. The only consistently noted complication in the neonatal experience has been an increased incidence of pulmonary hemorrhage.[116]

Future Directions

Current evidence suggests that surfactant will prove useful as an adjunctive therapy in pediatric respiratory failure, although likely with less spectacular results than those reported for neonatal RDS. Our current understanding of ARDS and other more specific forms of acute lung injury in children places surfactant dysfunction at the center of the disordered physiology but not as the cause thereof as in neonatal RDS. Surfactant replacement offers promise in improving the disturbance in lung aeration and gas distribution and allowing moderation of ventilatory support but not to "cure" the underlying injury. This may be adequate, however, because the mortality from acute lung injury in children appears to be decreasing[99,100] due, perhaps, to our better understanding of ventilator support.

Other questions remain. The best mode of delivery of surfactant needs to be determined. Most important, we need to better identify which patients will benefit and which will not by administration of surfactant. The development of better forms of synthetic surfactants—perhaps with genetically engineered surfactant-associated proteins—is likely in the near future and needs to be pursued to bring down the cost of this therapy. Depending on the size of the child, at the current market price of Survanta, one treatment may cost in excess of $5,000. This price does not represent the true cost of the drug, but, nonetheless, the natural surfactants are relatively expensive to produce, and the cost of the drug will probably remain high. Before embarking on wholesale acceptance of this therapeutic approach, it will be important to better determine which patients will benefit. To that end, a large, 50-center multiinstitutional trial of calf lung surfactant extract (Infasurf) in pediatric patients with respiratory failure was due to begin in the United States in the fall of 1998.

Table 3. Long-term Outcomes After Surfactant Administration Relative to Placebo.

Variable	Surfactant	Placebo	p value
Days of mechanical ventilation,* geometric mean (95% CI)	5.3 (3.1, 9.1)	10.7 (7.6, 15.1)	0.03
Days in PICU,* geometric mean (95% CI)	8.1 (5.2, 12.7)	14.4 (10.9, 19.1)	0.03
Days on oxygen,* geometric mean (95% CI)	7.6 (4.3, 13.4)	13.9 (9.8, 19.6)	0.06
Days in hospital,* geometric mean (95% CI)	14.0 (9.1, 21.5)	20.4 (15.8, 26.3)	0.12
Deaths	3	2	NS
ECMO	1	1	NS

Forty-six children with acute hypoxemic respiratory failure randomized to receive 80 mL/m^2 of calf lung surfactant extract (Infasurf) versus placebo. Children randomized to surfactant treatment had significantly fewer days on mechanical ventilation and days in pediatric intensive care unit (PICU).

*In patients surviving without extracorporeal membrane oxygenation (ECMO); excludes 5 who died and 2 placed on ECMO.

From reference 99, with permission.

PRODUCT SOURCES

Surfactants

ALEC, Britannia Pharmaceuticals, Redhill, United Kingdom

Exosurf, Glaxo Wellcome Inc, Research Triangle Park NC

Infasurf, ONY Inc, Amherst, NY

Survanta, Abbott Laboratories, Abbott Park IL

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Partial Liquid Ventilation and the Challenges of Randomized, Controlled Trials in Acute Respiratory Distress Syndrome

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Introduction
Preclinical Studies of Partial Liquid Ventilation
Partial Liquid Ventilation in Models of Lung Disease
Anti-Inflammatory Effects of Perflubron
Surfactant Production
Management of Secretions
Clinical Trials of Partial Liquid Ventilation with Perflubron
The Challenges of Randomized, Controlled Clinical Trials in Acute Respiratory Distress Syndrome

[Respir Care 1998;43(12):1086–1091] *Key words: acute respiratory distress syndrome, infant respiratory distress syndrome, partial liquid ventilation, perflubron, perfluorocarbons, surfactant.*

Introduction

A recent innovation variously termed perfluorocarbon-associated gas exchange or partial liquid ventilation (PLV) has simplified the technical aspects of using perfluorocarbons in the lung. It has been shown possible to fill the functional residual capacity of the lungs with perfluorocarbon liquid and to 'bubble oxygenate' the liquid in situ (in vivo) using a conventional gas ventilator.[1] This technique, gas ventilation of the fluid-filled lung, allows liquid to be used to recruit atelectatic lung and reduce surface tension at the alveolar lining. In expiration, the liquid functional residual capacity represents an incompressible reservoir of oxygen occupying alveoli that would otherwise collapse and allow intrapulmonary shunting. In inspiration, tidal volumes of gas purge that reservoir of carbon dioxide and replenish the supply of dissolved oxygen after the fashion of a very efficient bubble oxygenator.

This technique has been studied in animals and in patients with acute respiratory failure of various etiologies. Most recently, a randomized, controlled trial (RCT) of PLV in pediatric patients with acute respiratory distress syndrome (ARDS) has been undertaken. Enrollment in that trial was terminated early because of a dramatic decline in control mortality subsequent to a major amendment of study design. Although data from that trial have not yet been presented and cannot yet be published, the experience teaches valuable lessons about such trials.

Preclinical Studies of Partial Liquid Ventilation

Preclinical study of PLV has been very encouraging, providing a strong foundation for optimism about clinical applications of the technique.

Partial Liquid Ventilation in Models of Lung Disease

Tutuncu et al[2] have shown that rabbit lungs lavaged with saline to induce surfactant deficiency exchange gas more efficiently during PLV than during conventional gas ventilation. Leach and associates have shown this also to be the case in premature lambs with surfactant deficiency of prematurity,[3] and they have shown that PLV is compatible with exogenous surfactant therapy.[4] Wilcox et al[5] have studied lambs with surgically induced congenital left diaphragmatic hernia, and have shown that this lesion (which is complicated by surfactant deficiency) is amenable to treatment by PLV. In all of these models, lung compliance is improved by the presence of perflubron

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within the lung. Clearly, surfactant deficiency is highly responsive to PLV.

PLV has also been applied to piglets after intratracheal instillation of meconium.[6] In this model, Thompson et al showed that oxygenation and 6-hour survival were both substantially improved, though improvement in gas exchange was less striking and less rapid than in models of surfactant deficiency. Although meconium is thought to impair surfactant function, it is also known to obstruct distal airways. This mechanical issue contributes to the difficulty of rescuing animals after meconium instillation.

Numerous models of acute lung injury and ARDS have been studied. Papo and colleagues[7] showed that lung injury induced by intravenous oleic acid infusion is ameliorated by PLV. Nesti et al[8] showed that gastric aspiration–induced ARDS benefits from PLV with perflubron, and Hernan et al[9] demonstrated amelioration of acid-induced ARDS in large sheep. Improvement in histology was seen in the studies of Papo et al[7] and Nesti et al.[8] Hirschl et al[10] also documented improved histology in an oleic acid–injury model treated by tidal liquid ventilation.

When the normal lung is filled with perfluorocarbon, arterial oxygen tension ($P_{a(O_2)}$) falls by ~ 100 mm Hg. In surfactant deficiency, oxygenation improves after instillation of perfluorocarbon, and the lung then oxygenates blood as well as the normal, non-liquid-filled lung. This results from improved ventilation/perfusion matching. In fact, PLV with perflubron makes the surfactant-deficient lung function almost as though it were normal. But surprisingly, several inflammatory models also behave as though the lung was made to function normally after perflubron instillation. The combination of near-normal oxygenation and near-normal histology in Nesti's study[8] of aspiration ARDS and of improved histology in other recent reports of animal models of ARDS, suggests that perflubron may have anti-inflammatory effects distinct from the beneficial effects of PLV on lung function.

Anti-Inflammatory Effects of Perflubron

Smith et al[11] showed that alveolar macrophages are less readily stimulated to generate free radicals and hydrogen peroxide after exposure to perflubron. Perflubron also reduces neutrophil infiltration in the acutely injured lung.[12] It reduces phagocytosis but not killing by alveolar macrophages[13] and reduces nitric oxide production by alveolar macrophages in vitro.[14] Electron micrographs of alveolar macrophages exposed to perflubron in vivo reveal vesicles (that probably represent ingested perflubron) as well as loss of villous appendages. It is possible that pinocytosis of the liquid, which might be expected to internalize (as vesicle membrane) receptor sites that are normally bound to the cell surface, reduces the surface density of receptors that trigger inflammation. It is also possible that perflubron dissolves in the macrophage's cell membrane much like a volatile anesthetic, altering membrane function. Many volatile anesthetics alter inflammation, though their predominant effect is clearly to alter neuronal surface membrane function. Effects of perflubron on the alveolar macrophage are demonstrable after in vitro exposure. Such in vitro anti-inflammatory effects of perflubron represent a discrete mechanism from 'lung protective' anti-inflammatory processes (reduced volutrauma) that may also occur.

Because the clinical importance of these anti-inflammatory effects is not yet clear, there could be concern that perfluorocarbons might make the lung susceptible to nosocomial infection. Steinhorn and Sajan's[15] findings contradict this, suggesting that nosocomial infection is not facilitated by the presence of perflubron. Perflubron is, in fact, a bacteriostatic environment that does not support bacterial growth.

Surfactant Production

Perfluorocarbons are not miscible with aqueous solutions or gels, and surfactant is not readily soluble in perflubron. It is not likely that PLV would deplete the lung of phospholipid. Steinhorn et al[16] showed that, to the contrary, PLV with perflubron increases *de novo* synthesis of surfactant by normal lung. Similar findings apply to the immature lung studied by Leach et al.[17] It has been hypothesized that lung stretch mediates these increases in surfactant synthesis.

Management of Secretions

Secretions are not miscible in perfluorochemicals. Early clinical experience suggested that this might be a problem during PLV. Subsequent laboratory experience has shown that secretions may be effectively debrided from the lung by saline lavage during PLV. Recovery of small volumes of saline instilled into the 'dry' lung is minimal. Saline instillation may stimulate coughing and loosen proximal secretions, but it is not a very effective means of clearing secretions from the lung. During PLV, movement of perfluorocarbon in the airways appears to mobilize secretions toward the trachea. Tracheal instillation of saline tends to liquefy these secretions. Cessation of positive end-expiratory pressure or ventilator disconnect carries this debris forward into the trachea, where it can be removed by suctioning.

Clinical Trials of Partial Liquid Ventilation with Perflubron

PLV with perflubron (LiquiVent, Alliance Pharmaceutical Corp, San Diego CA) is an investigational technique, but is now in clinical trials for regulatory approval. Results

Table 1. Physiologic Responses to Partial Liquid Ventilation (PLV) in Premature Babies with Infant Respiratory Distress Syndrome

	Baseline	PLV (1 h)	PLV (4 h)	PLV (24 h)
OI	41.0 ± 7.0	22.4 ± 7.1	10.4 ± 2.2	8.9 ± 2.5
P_aCO_2	66.0 ± 12	56.0 ± 5.9	45.0 ± 5.4	44.8 ± 2.1
C Dyn/kg	0.22 ± 0.05	0.37 ± 0.04	0.37 ± 0.09	0.48 ± 0.19
MAP	16.6 ± 9.1	14.6 ± 0.91	12.4 ± 1.0	11.6 ± 0.89

OI = oxygenation index, $PaCO_2$ = arterial carbon dioxide, C Dyn = dynamic compliance, MAP = mean airway pressure.
Table adapted from data published in Reference 18

Table 2. Demographics of Adult Patients in Phase II/III Controlled Trial[21]

	PLV (n = 65)	CMV (n = 25)
Age (years)	43 ± 2	41 ± 3
>55 years old	28%	8%
P_{aO_2}/F_{IO_2} mm Hg	178 ± 12	198 ± 22
P_{aO_2}/F_{IO_2} < 200 mm Hg	62%	56%
200 < P_{aO_2}/F_{IO_2} < 300 mm Hg	26%	28%

PLV = partial liquid ventilation, CMV = conventional mechanical ventilation, PaO_2 = arterial oxygen tension, FiO_2 = fraction of inspired oxygen.

Table 3. Outcome for Adult Patients Who Received Partial Liquid Ventilation (PLV) or Conventional Mechanical Ventilation (CMV)[21]

	VFDs	% of patients with > 1 VFD	Mortality (%)
PLV (n = 39)	9.0 ± 1.4	62	26
CMV (n = 19)	4.1 ± 1.8	32	37

Patients were < 55 years old and had baseline P_{aO_2}/F_{IO_2} levels < 300 mm Hg
VFD = ventilator-free day

in infants with infant respiratory distress syndrome (IRDS) have been published[18] as have preliminary findings in children[19] and adults.[20] These trials document mortality rates lower than those for historic controls and show physiologic improvements in gas exchange and lung compliance; however, they lack companion control populations. There have also been three small randomized, controlled neonatal trials in target populations: premature neonates with IRDS, infants with congenital diaphragmatic hernia, and term neonates with respiratory failure. A large controlled trial has been conducted in pediatric patients with ARDS (currently under analysis). A controlled trial in adults with ARDS has been completed and its findings presented.[21]

The first corporate-sponsored study of perflubron PLV in the United States focused on the rescue of premature babies with IRDS.[18] On average, these patients had a gestational age of 28 weeks and weighed ~ 1000 g. To be enrolled, a baby had to be of 24–34 weeks gestation, with a birth weight between 600 and 2000 g, and be < 5 days of age. All patients were required to have failed at least one dose of surfactant. Enrolled infants were expected to have a very high risk of imminent death. The study group consisted of 13 patients who had failed, on average, between 2 and 3 doses of surfactant. Of these 13 patients, 7 survived and did well long term. Physiologic response is summarized in Table 1.[18]

The first pediatric Phase II trial[19] did not have a control group. On average, these patients were 4 years old and weighed ~ 18 kg. Most of them had pneumonia as a presenting diagnosis. At enrollment, their average alveolar-arterial oxygen tension difference ($P_{(A\text{-}a)O_2}$) was a little over 450 mm Hg. This $P_{(A\text{-}a)O_2}$ would have predicted about a 50% risk of mortality at the time that this study was undertaken. In this group of 10 patients, 8 survived. There were no serious unexpected adverse events that were deemed related to the drug.

Table 2 shows demographics of the adult Phase II/III controlled trial.[21] This trial compared PLV with conventional mechanical ventilation in adults with ARDS. It was intended that 2 patients receive PLV for every 1 patient randomized to conventional mechanical ventilation. The average age of this group of patients was slightly > 40 years, but there were numerous patients who were > 55 years of age. In the adult literature, it is quite clear that being old is disadvantageous if you get ARDS, and that above 55 years of age, mortality from ARDS is substantially higher than below 55 years of age. The study groups were unbalanced in that there were more older patients (> 55 years) in the PLV group (28%) than in the conventional group (8%). It is also important to note that not all of these patients had ARDS. Sixty-two percent of the patients in the PLV group and 56% in the conventional mechanical ventilation group had ARDS (a ratio of arterial oxygen tension P_{aO_2} to fraction of inspired oxygen [F_{IO_2}] of < 200 mm Hg). There were also patients who were not sick enough at entry to have what would be classified as acute lung injury (P_{aO_2}/F_{IO_2} between 200 and 300 mm Hg). The primary end points studied in this trial were ventilator-free days (VFDs), the number of patients who had VFDs, and the 28-day mortality rate. Mortality and VFDs were different between groups in patients < 55 years of age who had P_{aO_2}/F_{IO_2} of < 300 mm Hg (Table 3). There was also a difference between the two treatments in the percentage of patients who had at least 1 VFD, and there was a small difference in mortality. Thus, there is a suggestion that if one looks at the appropriate age and severity of illness in the adult population, using an outcome mea-

sure, one can see evidence of efficacy of PLV compared with conventional ventilation.

Between January 1996 and April 1997, 65 pediatric critical care programs participated in a randomized, controlled clinical trial of perflubron (LiquiVent) PLV for pediatric ARDS.* Enrollment in the trial was halted because study monitors noted an unexpected, sharp, and persistent fall in control group mortality after an amendment of entry criteria. Subsequent analysis of data for the 182 subjects revealed confounding factors and treatment differences between groups, which preclude comparisons of efficacy and outcome between study arms but do allow assessment of safety.

A detailed analysis of the trial is forthcoming but exceeds the scope of this discussion. At this time, it can only be reported that 28-day mortality was not statistically different between groups and that no safety problems were identified. However, the problems encountered in the conduct of this trial do teach important lessons for ARDS research, lessons that are applicable to virtually any interventional ARDS study.

The Challenges of Randomized, Controlled Clinical Trials in Acute Respiratory Distress Syndrome

Why have treatments and ventilatory strategies that appeared so promising in preclinical research had so little impact on the outcome of ARDS in RCTs?

The first issue in any ARDS RCT is identification of an outcome measure on which to stake the trial. The most obvious end point is, of course, mortality. One might well ask, "what good is it if it doesn't alter mortality?" But survival of the patient with ARDS is multifactorial: (1) The various risk factors (triggers) for ARDS each make their own separate contributions to mortality. Trauma, sepsis, and smoke inhalation each cause death by a variety of final common pathways, only one of which is ARDS. The patient with ARDS may succumb to his respiratory disease or, if that is prevented, may die of other associated processes (eg, head injury, cardiovascular collapse). (2) Most patients receiving intensive care die after a decision is reached to discontinue life support. This is a multifaceted decision and may have little to do with the ultimate reversibility of lung disease. (3) ARDS is often associated with the systemic inflammatory response syndrome (SIRS) or with multiple organ system failure (MOSF). These three syndromes (ARDS, SIRS, and MOSF) define constellations of findings. Like different parts of the elephant in the hands of a blind man, these defined syndromes may characterize the same patient from different perspectives or at different times. To alter mortality from ARDS, a treatment must also be effective against SIRS and MOSF; thus, any treatment proposed to alter mortality from ARDS should also propose to alter mortality from SIRS and MOSF. A drug to reduce ARDS mortality would be a drug for SIRS and MOSF mortality as well. (4) Mortality is a binary end point: the patient lives or dies. Comparison of group mortality by chi-square analysis requires large study populations, especially when mortality rates are substantially below 50%. This is highly problematic for diseases affecting modest numbers of patients and for expensive treatments. To circumvent this problem, various surrogates for mortality have been proposed that reduce outcome comparisons to contrasts of continuous variables using *t* tests. VFDs is an example of such a surrogate. It remains to be seen whether VFDs are a better end point than mortality, for, as with ARDS, the determinants of VFDs are multifactorial.

Population heterogeneity is another factor that confounds ARDS trials. The population of patients with ARDS consists of patients at ultra-high risk of mortality from their lung disease and of patients at very low risk of pulmonary mortality. Those at high risk may remain at high risk even if their ARDS is effectively treated because they often suffer from other serious problems. Those at low risk have a 'signal-to-noise' ratio that is too low for study and dilute the signal of any other subgroup that might benefit from treatment. The patients to study are those of intermediate risk of pulmonary mortality, and that population can be subdivided further into those having exclusion criteria, those having other reasons to die, those who might respond to the treatment (but will also respond to other treatments available to the control group), and those who will only respond to the trial therapy. The entire signal in a mortality study rests in this last group, patients who will only respond to the trial therapy (which is, alas, generally a group too small to study and impossible to identify prior to enrollment). Eagerness to enroll large populations tends to bury the signal in noise.

Most ARDS trials are difficult to blind. In neonatal nitric oxide trials, disguising the gas canister does not prevent the clinician from guessing the treatment arm from serial measurement of methemoglobin levels. How do you blind surfactant therapy, PLV, or a trial of low lung stretch? Any intervention that acutely alters physiology, even if the physiologic parameter is not the end point, gives itself away, and it doesn't matter that the clinician only guesses right most of the time. Statistically, the trial is poorly blinded if one can 'usually' guess the group assignment. Some of the effects of lack of blinding are obvious: (1) It introduces potential treatment bias. Investigators would not be in the trial unless they wanted the intervention arm to win. On the other hand, (2) the unblinded trial intervention draws special attention to the treated subject. This

*Presented at the Pediatric Critical Care Colloquium, September 16, 1998, Chicago, Illinois.

may enhance care, exaggerate adverse event reporting, or both. It certainly prompts the investigator to attribute treatment causality to adverse events, whether that is the case or not. (3) For instance, in the PLV trial, lack of blinding had a special impact on parents of subjects assigned to the control group. Nobody enrolls their child in a clinical trial in hopes of getting into the control arm. What incentive is there to enroll in an RCT other than to reap potential benefit from the experimental treatment? So both the clinician investigator and the parent are biased to offer additional aggressive therapies (experimental or otherwise) to the control patient. The unblinded nature of the PLV trial, for instance, led to a dramatic imbalance in application of rescue therapies (favoring the control group by a factor of 2:1) and to a high overall use of combinations of rescue techniques in control subjects.

The use of rescue therapies is but one example of treatment heterogeneity within and between groups. There are many different algorithms for ventilator management, and there are other, more subtle management issues that may influence outcome. These are extremely difficult to regulate during an RCT. The less effectively these sources of noise are regulated, the more difficult it becomes to show differences between treatments. It has been proposed that ARDS trials employ computerized algorithms of ventilator management. Unfortunately, the two arms of a trial may require very different ventilator algorithms. Would the existence of separate computer algorithms for the two arms of the study introduce a special bias into such a trial?

Some RCTs involve a learning curve that, of itself, acts against the treatment group. There seem to be two types of learning curves: The investigator may get better at a technique over time, or the collective wisdom of the investigative team may grow over time. Obviously, results of a new technique in any investigator's hand will improve as he or she gathers personal experience. It may be less obvious that we learn and make progress collectively. Over the course of time, investigators have learned how better to use the oscillator. After studying numerous volutrauma-sparing algorithms of mechanical ventilation, we may be getting closer to techniques that are, indeed, effective. One must be cautious about approaching definitive trials before climbing both of these learning curves.

In any multi-institutional trial, there will be differences among sites. Some sites will be enthusiastic about the experimental treatment and will enroll as many patients as possible, generally at lesser severity of illness. Other sites will be timid and enroll only those patients for whom the trial represents a last resort. Certain sites only care for high-acuity patients. Other intensive care units have a consistently low acuity level. Obviously, sites like your own always provide excellent care, whereas others do not. Couple this heterogeneity among sites with enrollment imbalances and you have major problems. What if low-acuity sites enroll more patient in one arm of the study than in the other? Will that not influence the results of the trial? In essence, unless enrollment procedures are carefully designed, a multi-institutional trial may represent randomization of a few sites as opposed to randomization of large numbers of patients.

Over time, treatments change. Any trial that spans too large an interval of time is likely to be confounded by changes in therapies other than the treatment under study. Some of these changes may be more profoundly effective than the intervention under study. In unblinded trials, these new treatments will tend to work their way into the control population earlier than into the treatment group. So rapid enrollment and a short trial are to be desired. On the other hand, rapid enrollment often depends upon loose enrollment criteria. This fosters noise. ARDS is such a diverse syndrome that strict criteria are essential to the conduct of a mortality trial. This means slow enrollment and long trials.

Finally, power to show a difference is very dependent on study size. Likelihood of finding a beneficial effect of treatment (if one exists) is never 100%. The larger the sample size, the more likely it is that a difference, if one exists, will emerge, and that the difference that can be shown to be statistically significant will be smaller. But power (sample size) costs money. ARDS trials are extremely expensive. Depending on the intervention, they may cost upward of $20,000 per patient. Some adult trials will require prohibitive quantities of drug. Not many RCTs of 500 ARDS patients will ever take place. The investment and the financial risk are both excessive.

The current process for 'finding a cure' emphasizes identification of a new treatment that is better than all others, whether the others are applied collectively or separately. The control group has access to all approved therapies and perhaps to some experimental ones. Even if the treatment group has equal access to all therapies, which in an unblinded trial is unlikely, success in a mortality trial demands a massive improvement over other accepted treatments. Moreover, the establishment of one such 'winner' could prevent other useful therapies from emerging by raising the gate for acceptance and preventing approval of new treatments that might make special contributions to ARDS management yet not produce a further measurable increment in survival.

We believe that ARDS trials can succeed. But they must be carefully planned, and they must target reasonable end points.

Intensive care is a problem-oriented venture. Though intensivists like to think we set our sites on ultimate survival, we generally approach patient care in a problem-oriented fashion. At any moment, we treat to raise oxygen tension, improve cardiac output, reduce intracranial pressure, kill bacteria, quench inflammation, stop blood loss,

or eliminate pain. Seldom do we know that any specific therapy will determine outcome. End points of ARDS trials should combine proof of safety with a measurable effect that represents a desired end, like recruiting lung, improving oxygenation, or quenching inflammation. Treatments should be evaluated on the basis of our reasonable expectations of them (on the basis of how we hope to use them) not on an as-yet-unfounded belief that there will be one magic bullet for ARDS.

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1997 Donald F Egan Scientific Lecture

The 'Whys' and 'Wherefores' of Measuring Outcomes in Respiratory Critical Care

William J Sibbald MD

Thank you very much, Madame President. It is a pleasure to be with you and your organization today. It is also an honor to be part of your Congress and to bring to you a message about outcomes measurement and health services research. As health care professionals, you have become increasingly familiar with these terms over the last few years. We know that your future clinical activity in respiratory care will become increasingly dominated by a requirement for knowledge in the health services field, particularly in terms of measuring the impact of your care processes.

I am indebted to the sponsors of this lecture, which was named for Dr Egan, one of the pioneers in the field of respiratory care. In this lecture, I hope to recreate the excellence that he gave to us in his contributions to your discipline.

In looking for ways to share with you the passion I feel about health services research and to help you understand why it is becoming an important part of our professional paradigm, I am going to paraphrase a quotation to create a perspective: "We trained hard, but it seemed that every time we were beginning to form up into teams, we would be reorganized. I was to learn later in life that we tend to meet any new situation by reorganizing—and a wonderful method it can be, for it creates the illusion of progress, while at the same time producing confusion, inefficiency, and demoralization." While this is probably an apt description of what you and I feel as professionals in health care today, the sobering fact is that this statement is attributed to Gaius Petronicus Arbitrar in the year 210 BC.

Nevertheless, the take-home message of this quotation is that change will be a feature of the health care landscape for the foreseeable future, and I will argue that our responsibility in coping with change includes a commitment to measure, analyze, and interpret what we are doing so that we can provide the highest quality and most affordable health care possible. In this context, today's address will focus on health services research and outcomes measurement. I will explain why we need this activity by showing some examples, and I will also emphasize the concepts of *evidence-based decision-making* and *research transfer*.

Let us begin by asking, "Why would you invite me to talk to you about health outcomes research?" While I have argued that change should be anticipated as a normal part of health care, the pace of current change activities in all western nations is phenomenal. Part of that change is a challenge to our professional organizations to lead improvement in clinical effectiveness. Clinical effectiveness can be defined as: ". . . for the right patient, doing the right thing at the right time in the right setting by the right health care provider, using the right resources."[1] Above all, improving clinical effectiveness is a sensible way for us to manage the imbalance that exists between available resources and resources required to care for our patients. Now, here is another definition for you—health services research is a multidisciplinary field of inquiry, both basic and applied, that examines uses, costs, quality, accessibility and delivery, financing, and effects of health services for individuals or populations.[1] This is the broad discipline under which health outcomes research falls.

In addition to measuring outcomes, there are other core competencies in the health services domain that our system needs at this time, including risk stratification, assessment of cost-effectiveness, measurement of the quality of life and the quality of care, and economic evaluations. If these are skills that are increasingly required by today's respiratory care leader, then where have we built this knowledge into our training programs? When you did your professional training, how many of you received course-work in these competencies?

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You are not alone in being ill-prepared for the new skills required in our health system. In a recent training session with a group of final-year residents, participants said, "We go out and apply for a job and we are asked what we know about risk stratification, assessing cost-effectiveness, measuring outcomes, economic evaluations, quality of care, and evidence-based medicine." They felt that the leaders of our academic health centers had let them down by not providing the broad-based education in the core competencies of health services that is increasingly required to practice in today's health system. I have a challenge to pose to the leadership of your Association: Consider the development of training opportunities for your membership in the health services competencies. Create a sequence of training opportunities in measuring outcomes, risk stratification, cost-effectiveness, quality of life, quality of care, and evidence-based health care. Until we learn and practice these skills, our health system will contract out to other organizations to do and interpret the measurements, and who will then advise us how to improve our clinical effectiveness activities? The concern I have with this approach is that the ability to truly understand the question, to meaningfully interpret and analyze the data, and then to act on what it tells us requires a large measure of '*local, clinical* flavor.' Contract research organizations simply cannot give this meaningful aspect to the process of outcomes measurement. If we have the knowledge, we can own the activity—and then, we can more appropriately be held accountable for our actions.

One of the objectives that your incoming president suggested for you might be reinterpreted to challenge us to "learn together—this thing called health services research—so that we can be in charge of the data." By being responsible in knowing how to collect, analyze, and interpret data describing what we are doing, we can then apply our professional knowledge to ensure that our patients receive clinically effective care.

Let me build upon these opening comments with some clinical examples. Remember the annual 'quality project.' Like you, once a year I get a letter from one of the vice-presidents that says "Congratulations. You have been selected to champion an annual quality project." Since senior management has heard from other administrative colleagues that 'readmissions' can be used as an indicator of performance, in this scenario, *you* are asked to chair a committee to review intensive care unit (ICU) readmissions and then to create guidelines that would minimize this problem. What do you do? The evidence-based medicine paradigm is a good starting point.

Evidence-based medicine emphasizes the need to base clinical decision-making, wherever possible, on the results of rigorously controlled investigation and the need for caution when clinical decisions rest only on the results of data from nonhuman studies and uncontrolled observations.[2]

Table 1. Steps in The Process of Applying 'Evidence' to Your Practice.

Create a focused clinical question
From the background of your clinical problem, create an unambiguous question against which you could evaluate the content of a search
Systematically search the literature
Identify the most appropriate evidence source to search, for example, MEDLINE
Assess the validity of studies identified
Using the process of critical appraisal, review the evidence and rank it according to its strength
Apply the results to your clinical practice
Create a process to implement the evidence
Evaluate performance
Always 'close the loop' by determining if the outcome gained is as expected from your evidence search

When applying the evidence-based medicine paradigm to either clinical or administrative problems, the first step is to create a clear and unambiguous question about the issue (Table 1). Perhaps the question might be formulated as, "What is a readmission to the ICU and what are the factors that are known to influence ICU readmission rates?"

As Table 1 demonstrates, once the question is formulated, the next task is to select the most likely resource to answer the question. We are increasingly aware that printed material in textbooks may be out of date when published because of the slow turnaround from putting the content on paper to getting the product out to front-line decision-makers. In this electronic age, there are solutions in that the most recent knowledge can be made available from the National Library of Medicine (and other databases) through MEDLINE. For those of you who do not normally access MEDLINE in your hospital, the government has made a commitment to your transfer of knowledge by creating an electronic resource, **PubMed.** So, as you begin thinking about the quality project on ICU readmissions, the first thing you need is the **PubMed** uniform resource locator (URL): **http://www.ncbi.nlm.nih.gov/PubMed/.** The American Association for Respiratory Care home page **(http://www.aarc.org)** provides direct access. **PubMed** is a free, on-line, National Library of Medicine–sponsored environment where we can go via the World Wide Web to ask questions and discover evidence.

In accessing this universal resource locator, you can also find learning tools about how to create a search strategy. In addition to this learning environment, there are good papers that explain how to make an electronic search.[3,4] And perhaps as a first step, visit your hospital librarian, a professional who has been trained in searching the National Library of Medicine's database and who will not only help you formulate and search the question but

Table 2. Levels of Research Approaches To Answering Questions. Rigorous Study, As Employed in a Randomized Controlled Trial (RCT), Is More Likely To Identify 'Truth' in the Experimental Question Than Are Retrospective or Clinical Case Studies.

Level 1	Large RCT Little chance of statistical errors
Level 2	Smaller RCT More chance of statistical errors
Level 3	Cohort studies, concurrent controls
Level 4	Retrospective studies, historical controls
Level 5	Opinion and personal experience (ie, case studies)

will help you understand how to analyze the results of your search.

In returning to our question, when we searched MEDLINE for evidence of previous research on ICU readmissions, we discovered a number of published articles. Table 1 shows that the next step is to critically appraise the research work that is found to determine the validity and truthfulness of the observations. In any scientific question, remember that there are a number of approaches, ranging from a randomized controlled trial to case reports, to determine the answer. Table 2 lists some of the different approaches to answering scientific questions, and it explains why evidence from a randomized controlled trial should be accepted as stronger evidence than descriptions contained in case reports.

The process of critical appraisal is another of the important contributions of the evidence-based medicine paradigm. The *JAMA* series on evidence-based medicine, which was published over the past 5 or 6 years,[5] is a rich source of knowledge on how to make a critical appraisal. In this series, instruction is provided on how to critically appraise various articles that constitute the health care literature—for example, "How to Use an Article about Therapy Or Prevention. . ."[6] and "How to Use an Article about a Diagnostic Test. . ."[7] Full reference to all of these articles can be found by simply searching **PubMed** under the terms 'evidence-based medicine' and 'review.' Another source of information regarding evidence-based medicine, how to do it, and how to use it is found on the Web site for our Academic Health Sciences Network at the University of Western Ontario (**http://ahsn.lhsc.on.ca**). There are also a number of textbooks and workbooks that you can access for learning.

Returning to our question about ICU readmissions, it is important (as in other research questions) to use the critical appraisal process and ask 3 fundamental questions of published work that you find via MEDLINE searches:[1] Is the evidence valid?[2] What is the evidence?[3] And, can the evidence be applied to the care of my patients? In the *JAMA* evidence-based medicine series, you will find descriptions about how to critically appraise articles on therapy, diagnosis, harm, prognosis, overviews, practice guidelines, decision and economic analyses, and more. The articles tell you why it is important to make a critical appraisal and how to do it. An important component of these articles is their summary tables, which can be photocopied, laminated, and put in your pocket for easy reference, and which highlight key questions to ask of any article in determining its validity.

In again returning to our question about ICU readmissions and remembering that we had identified by our MEDLINE search a number of articles discussing this topic, I applied the approach to their evaluation as described by Naylor and Guyatt in their *JAMA* article, "How to Use an Article about a Clinical Utilization Review."[8] Naylor and Guyatt provide the foundation for an approach to understanding articles on health care utilization that easily applies to articles describing ICU readmissions. Table 3 lists the different questions that need to be answered when analyzing an article about clinical utilization review. Of importance when applying these questions to the published articles discovered in our search about ICU readmissions, most of the articles were retrospective studies and therefore open to bias. At the conclusion of this level of our investigation, we can agree that evidence put forward by colleagues in peer-refereed literature describing ICU readmissions could be improved upon because of its retrospective nature. In fact, one of the 'opportunities' in the evidence-based medicine paradigm is the discovery that you can contribute to evidence generation: Where you have asked the question and cannot find good, high-level evidence, consider designing an approach to provide this evidence for colleagues to reference in the future.

In the latter context, we determined there were many ways to enhance the validity of questions relating to ICU resource utilization. One of the approaches we have found most gratifying is the development of an ICU network—a collaboration of ICUs of different sizes and roles in our health system—to share knowledge about what we are doing and what works. I began to appreciate the strength of this approach after working with our provincial government on a strategic planning exercise that was summarized in a report from our Working Group on Critical Care Medicine.[9] In this report, we found that hospitals in general provided good episodic care to critically ill patients. We also found little coordination among care providers and the institutions and agencies involved. We felt there were great opportunities for more efficient use of resources, but that more effective care would result only by making improvements in service coordination, communications linkages, patient transportation, guidelines use, and *availability of data on resources and utilization*. From this initiative, we created a network of ICUs that had the following objectives:

Table 3. Abridged Questions to Apply to Articles about Clinical Utilization Review.

Are the criteria valid?
Was an explicit and sensible process used to identify, select, and combine evidence for the criteria?
What is the quality of the evidence used in framing the criteria?
If necessary, was an explicit, systematic, and reliable process used to tap expert opinion?
Was an explicit and sensible process used to consider the relative value of different outcomes?
If the quality of the evidence used in originally framing the criteria was weak, have the criteria themselves been correlated with patient outcomes?
Were the criteria applied appropriately?
Was the process of applying the criteria reliable, unbiased, and likely to yield robust conclusions?
What is the impact of uncertainty associated with evidence and values on the criteria-based ratings of the process of care?
Can you use the criteria in your own practice setting?
Are the criteria relevant to your practice setting?
Have the criteria been field-tested for feasibility?

Table adapted from Reference 8

Table 4. Four Questions to Define an Approach to "Quality Improvement"

What are we doing now?
Data collection—inputs and outputs
How well are we doing?
Benchmarking (comparing care processes among peer institutions)
Can we do better?
Comparing resources used and outcomes achieved in peer institutions and in the literature
How can we best achieve these improvements?
'Research transfer'

1. To establish and maintain a registry of the structure and activity of the critical care facilities in our region.

2. To establish and maintain a registry of the resources used and outcomes achieved.

3. To develop data analyses and reporting mechanisms that described, compared, and evaluated current activities.

4. To develop specific protocols designed to examine and improve utilization management and total quality management in the member critical care facilities.

Key to this initiative was an understanding that collaboration could *identify and share best practices*. From a small beginning, the Critical Care Research Network (CCR-Net) in Ontario has now grown to include in excess of 50 hospitals in its various activities. An early commitment was to agree on a template that would drive our health services research activities. In talking to my brother-in-law, I learned that quality-improvement templates in companies such as General Motors include four basic questions (listed in Table 4), and the network hospitals quickly adopted this approach to their questioning. Let me explain in more detail by returning once again to our initial problem—ICU readmissions.

Remember that in the model I presented, you, as the lead in the ICU readmission project, had been asked to create guidelines to minimize the problem of readmissions. What this quality-improvement model tells us is that it is wrong to conceptualize the solution (ie, create a guideline or pathway) until you understand the scope of the problem. Has that ever happened to you? Next time somebody asks you to sit on a clinical guidelines committee, ask them if they can describe the scope of the problem that you are addressing. Encourage them to ask the questions, "What are we doing now?" and "Can we do better?" before they embark on the solution! I have found that, in many guideline activities, the development of rationale to support guideline development (ie, identifying the magnitude of the problem and whether improvement can be achieved) has not been thought out in advance.

In the quality-improvement model outlined in Table 4, the first question, "What are we doing now?" requires identification of a database. In our CCR-Net, the first thing we did was meet with our community hospital partners to identify a *minimum data set*. This database, collected in an ongoing and retrospective manner, allowed us to go back and ask individual questions of it. For example, "What is the magnitude of ICU readmission and does it differ between hospitals of different sizes and with roles in the system?" Once we identified the scope of our readmission rates, *benchmarking* could then be undertaken to help determine if we have a problem at all. Benchmarking is another part of the outcomes process—comparing and describing differences within and between peer hospitals (Table 5). Benchmarking often requires that the methodologist be sensitive to the fact that some hospitals have cases of different illness severity than others. Therefore, benchmarking requires that adjustments be made to the database for illness severity, among other issues, such that all hospitals that are part of the benchmarking process can agree that conclusions may be generalized to all. In addition to benchmarking in your own data set, benchmarking can also be done with published work that is found in MEDLINE and other databases.

Now returning to our question, analysis of readmissions in CCR-Net member hospitals revealed that 4.6% of patients discharged from our ICU were readmitted during the same hospitalization (a percentage similar to that in literature reports); 45% of these patients were readmitted because the initial disease recurred, and 40% had new complications. Patients with gastrointestinal and central nervous system diagnoses had the highest rates of readmission.

Table 5. Steps in the Benchmarking of Clinical Process Data.

Define a process of interest
Gather data to describe the process
Compare process with that of peers
Identify factors that drive superior performance
Adopt these factors
Assess impact

Now, let me summarize where we have come to on the quality-improvement project scenario relating to ICU readmissions:

1. First, we defined what we meant by an ICU readmission, using experience drawn from the medical literature, which, of course, was critically appraised.

2. Next, we set up a system to measure readmission rates in our ICU and then benchmarked it with readmission rates in ICUs similar to ours and with the literature (after appropriate critical appraisal).

3. We then had to determine if a problem existed—that is, we asked if our readmission rates needed to be improved.

4. Finally, we established a process to identify specific activities that could be used to reduce our readmission rates. In this process, we analyzed factors in individual cases that might have led to readmission, and we learned from other people's experiences in critically-appraised literature as well as from 'best practices' determined by discussions with our partners in the CCR-Net. Then, we discussed and implemented care maps and guidelines to specifically deal with the activity we found that promoted readmission.

In summary, this quality-improvement activity was in reality an outcomes research project, ". . . the set of activities involved in generating, collecting, analyzing, and applying information about the results of outcomes in critical care of an intervention (or its lack) on a previous state of health."[10]

We have found that the collaboration of hospitals on outcomes research projects also leads to more effective implementation—the participants work together to discover new knowledge and then write up the data for submission to a peer-reviewed journal. The article will come out under *their* name. They assume ownership for the findings on solutions to readmissions. With this ownership, they create change that is sustainable—they don't need senior management to tell them how to do things because *they've* discovered the research, *they* own it, and *they* will make the change.

Let me show you another example of the way outcomes research can be practiced to drive improvements in clinical effectiveness using a 'network' approach. At one of our meetings, members of our community hospital partners in the CCR-Net asked about the process by which we feed critically ill patients in our ICU. One of them said, "My hospital CEO was just recently visited by somebody from a new enteral feeding company who says that they can do things cost-effectively, and they want me to change my current contract. But I think it's going to cost more! What do I do? My budget can't afford it."

In addressing this to the network, we then returned to the quality-improvement model (see Table 4). Again, the first question to ask is, what they were doing at this time in terms of enteral feeding in their ICU? Not many ICUs rigorously record the methods employed in feeding their patients, and the CCR-Net member hospitals were no different. With this challenge, for 3 months, members of the CCR-Net gathered data on who was being fed, for how long, and with what. While they gathered data, we designed a process to bring them together to learn skills in the evidence-based medicine paradigm. Specifically, we taught them how to search the literature to find out what other ICUs were doing in terms of feeding. We then taught them how to critically appraise this work so they could use only the work that was valid. From this experience, they were able to find published work, which, after critical appraisal, was determined to be high-level evidence.

Thus, they measured what they were doing and at the same time undertook a literature review to determine what they should be doing—comparing the two allowed them to conclude 'appropriateness.' From their collaboration on a collection of data describing feeding and compared with what the literature said they should be doing, the network members found *variation* among their ICU practices. While there are many reasons offered to explain variation in practice, outcome researchers agree that this is a rich field for analyzing change opportunities: Variation usually means that improvements can be applied to enhance clinical effectiveness.[1,2]

Returning to the clinical problem, namely, how should we be feeding our ICU patients, we found that variation allowed us to convince each other that a common clinical guideline applied among all CCR-Net hospitals might lead to improved care. Remember that clinical guidelines are systematically developed statements to assist practitioners and patients make decisions about appropriate health care for specific clinical circumstances.[11] The most important part about clinical guidelines is that they be based on evidence, not on opinion. Remember, you cannot presume that a guideline will work. You always have to evaluate it.

For us, the exciting next step was to determine if the process in fact worked. Therefore, we set up another research project, in which 8 hospitals were stratified to receive the guideline, and 8 others were not provided this tool. We are currently measuring the change in appropriateness of feeding between these two groups of hospitals to determine if this user-generated clinical guideline process

can indeed improve the appropriateness of care (in this instance, around the feeding of ICU patients).

As we have progressed in sharing the evidence-based paradigm, outcomes research, and other areas of health services with our hospital partners in the CCR-Net, we have committed some of the techniques and the knowledge base to our Web site **(http://ahsn.lhsc.on.ca).**

Another learning opportunity for us was the discovery that our community hospital partners valued the opportunity to undertake a collaborative clinical research effort with us. At the same time, our university also valued the professional time they put into this. We therefore went to our university and said, "You know, we have a number of professionals in the community—respiratory therapists, dietitians, and nurses—helping us gather research data. As they do that, they learn about outcomes research and about evidence-based medicine." The university therefore allowed us to create a continuing education program around these activities—another win-win outcome.

I want to tell you about another scenario, one that helps you appreciate the strength of outcomes research. One of our ICU physician leaders requested the purchase of end-tidal carbon dioxide (CO_2) monitors to monitor patients with respiratory failure in the ICU. He had been in a meeting in which he had been told that guidelines had been approved by one of the professional societies, indicating that all patients requiring mechanical ventilation should be monitored by end-tidal CO_2 monitors.

At the same time, another of our ICU physician colleagues requested that we consider the purchase of noninvasive ventilators because he had recently been told they were cost-effective. Let us agree, for the sake of argument, that our budget is capped this year, that we cannot afford both end-tidal CO_2 monitors and noninvasive ventilators. In this case, how do you reconcile the needs of both of these colleagues? Well, this is where evidence-based medicine and outcomes research can, once again, help. First, we brought both colleagues together and challenged them to find the evidence that purchasing and intelligently using the technology they requested would improve our clinical effectiveness. We asked them to return to the series of questions outlined in Table 1 and to then create a business case for our ICU committee.

In the case of noninvasive ventilation, our physicians pulled together colleagues who searched the literature and, after critical appraisal, did not find one clinical trial that unequivocally demonstrated that noninvasive ventilation would improve care or reduce costs with no change in care for patients with respiratory failure. However, what was found was a number of smaller trials that allowed synthesis in the form of a meta-analysis. In this approach, the team demonstrated that noninvasive ventilators applied to patients with respiratory failure would improve care and reduce costs—that is, they were cost-effective.[12]

On the other hand, the physician colleague who requested end-tidal CO_2 monitors found no published work in the literature describing improved outcomes (or reduced costs) in ICU patients with ventilatory failure who required mechanical assistance and who were concurrently monitored with end-tidal CO_2 monitors. Therefore, he began the process of assessing this technology in his own ICU and, to his chagrin, found that in the very patients he felt required monitoring, namely, those with acute respiratory failure, the end-tidal CO_2 showed poor precision and bias with the arterial partial pressure of carbon dioxide.

What we were left with was a decision to consider purchase of noninvasive ventilators with evidence that they were cost-effective versus a decision to purchase end-tidal CO_2 monitors that might not be as reliable as the reference standard (ie, the arterial blood gas). It was an easy decision for the hospital, most importantly because it was based on evidence. This is another reason that using outcomes research and evidence-based medicine is appealing—it helps us make better business decisions.

Now, before I summarize, let me share another exciting experience. We can all agree that there is little data describing the process of ventilatory care in our ICUs. With support from Siemens, we created a model by which appropriately encrypted and secured data describing mechanical ventilation in the participating ICUs could be gathered over the Web. In this pilot project, we have 10 hospitals gathering data every day on the Internet. The respiratory professionals record who is being ventilated and why. We also have a chat page for them to talk to one another about individual problems they might have. We think that it will take about 8 months of data collection before we have enough patients in the database to allow the participating hospitals to benchmark the data with each other. As this is only a pilot project, access to this URL is limited until we determine that the process is valid and secure.

Now let me summarize what I hope has improved your knowledge about evidence-based health care and outcomes research: Outcomes research provides a fuller understanding of what does and does not work in medical diagnosis and therapy, thereby enabling both patients and physicians to make better-informed, more efficacious, and more efficient health care decisions. Outcomes research is a core foundation upon which the evidence-based movement has been built. There is no ownership in outcomes research. It belongs to you. You are the outcomes researchers.

I would challenge you as a professional association to include the learning of skills in health services, including outcomes research, as a part of your continuing education agenda for the future. Mark Twain said, "There's something fascinating about science—you get such wholesale returns and conjecture out of such a trivial investment of fact." Well, that's not what outcomes research is. Out-

comes research is discovering and then applying this to improve clinical effectiveness.

Humans are almost unique in having the ability to learn from the experience of others, and they are also remarkable for their apparent disinclination to do so. I am saying to you, "Share your knowledge with each other. Become outcomes researchers as a group and find a way to share your best experiences, your best practices with each other."

I thoroughly enjoyed the opportunity of visiting with you and sharing some of the excitement that I feel for this field. I hope that someday in the future, you will invite me back and share with me some of the message that I hope I have left with you. Thank you very much.

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Asthma Epidemiology: Principles and Methods. Neil Pearce, Richard Beasley, Carl Burgess, and Julian Crane. Hardcover, 266 pages. New York/Oxford: Oxford University Press, 1998. $49.95.

Interest in the epidemiology of asthma has heightened because of apparent increases in the prevalence and severity of asthma, differences in prevalence rates in different regions, and epidemics of asthma mortality. This book aims to bring together in a single text those concepts of epidemiology relevant to studies of asthma. The authors highlight these concepts with numerous illustrations from published descriptive, case-control, cross-sectional, and longitudinal studies, demonstrating the principles, methods, and complexities of determining the epidemiology of asthma, including its prevalence, development, persistence, severity and, mortality.

Part I covers basic principles and introduces readers to unfamiliar and easily confused terms, such as incidence proportion, incidence odds, rate ratio, risk ratio, odds ratio, and relative risk, together with formulas for calculation of these statistics with standard errors and p values. Issues of study design, including precision, validity, and effect modification, are reviewed.

In Part II, the authors illustrate measurements of asthma prevalence by symptom questionnaire and physiologic measures, including airway responsiveness, and discuss recent internationally standardized studies in adults (European Community Respiratory Health Study, ECRHS) and children (International Study of Asthma and Allergies in Childhood, ISAAC). Results of these studies are not included. Measurements of asthma morbidity—symptoms, physiologic changes, health service utilization, medication usage, quality of life—are reviewed and illustrated by trials of pharmacological and other interventions. The longest chapter, with over 40 pages of text and some 280 references, deals with measurement of asthma risk factors, including studies of indoor and outdoor allergens and air pollutants, occupational exposures, genetics, intrauterine factors, atopic status, diet, viral infections, and environmental tobacco smoke exposure. The authors do not attempt to provide comprehensive coverage of these risk factors, but rather, examples are used to illustrate principles and methods of study.

Part III deals with asthma mortality, with a short chapter on time trends in asthma deaths, and a substantial chapter on causes of asthma death. The dominant focus of this chapter is studies of pharmacological risk factors, particularly short-acting β-agonists, especially fenoterol. This chapter takes the reader through the authors' defence of the validity of their case-control studies, leading to the conclusion that use of fenoterol increased the risk of asthma death in New Zealand. In contrast, nonpharmacologic associations with asthma mortality are given only 4 pages of this 32-page chapter. It is of interest that, while the association between fenoterol use and mortality is covered extensively in this book, the authors' controversial hypothesis that this association is due to cardiac toxicity of fenoterol is not mentioned.

This book is not a text for readers seeking results of studies of asthma epidemiology, but rather is for those wanting an understanding of how epidemiological data are obtained and calculated, what different epidemiological terms mean, and what factors influence these measurements. The target audience will be respiratory physicians, allergists, pediatricians, nursing and technical staff interested in asthma care and wanting a basic understanding of epidemiology, or epidemiologists becoming involved in studies of asthma.

Overall, the authors have achieved their aims of illustrating principles and methods in epidemiology pertinent to the study of asthma, with a well-written consistent style and extensive referencing of published studies used as illustrations. Readers may find the chapter on study design options somewhat technical, particularly the pages of statistical formulae, but the message of the chapter can be understood without following the details of the mathematical calculations. A few tables are difficult to follow. Table 2.2 introduces notation that will be confusing to the nonstatistician reader, although the meaning of notation becomes clearer when illustrated in a hypothetical study in Table 2.3. Occasionally terms are introduced in text or tables without explanation, eg, Page 38 discusses a nested case-control study not previously defined. Similarly, in example 5.11, the terms 'rating scale' and 'standard gamble utilities' are used without explanation or reference to a source document.

The book is well produced with clear typeface and is easily read. Tables are generally clear and well referenced, as are the few figures. A useful index is included. Up-to-date references are placed alphabetically at the end of each chapter. A number of typographical errors were detected, but these were minor.

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Diagnosis and Treatment of Symptoms of the Respiratory Tract, Richard S Irwin MD, Frederick J Curley MD, and Ronald F Grossman MD, Editors. Hardcover, illustrated, 637 pages. Armonk NY: Futura Publishing Co. Inc, 1997. $125.00.

Symptoms referable to the respiratory tract are the most common reason for patients to seek outpatient medical care in the United States. Some of these symptoms, such as dyspnea, chest pain, and hemoptysis, may be manifestations of an immediately life-threatening disease process. Others, such as cough, epistaxis, and headache are generally less serious, but no less troubling to the patient. Symptoms such as snoring or halitosis may be more objectionable to companions than to the afflicted patient. In each case, the challenge for the clinician is to efficiently determine the cause of the symptom, recognize serious underlying conditions when they are present, provide specific therapy directed at the underlying cause when possible, and offer nonspecific symptom relief. *Diagnosis and Treatment of Symptoms of the Respiratory Tract* is intended to guide clinicians through this series of decisions for each of the major symptoms of the respiratory tract. On the whole, the book is a tremendous success. Its strength lies in its symptom-oriented organization, its consistently scholarly approach, and its collection of commonly managed problems together with poorly under-

stood and unappreciated symptoms in a single volume.

Drawing on their experience with studies of cough and dyspnea, the editors have developed a format that is extremely useful clinically. Each chapter focuses on a symptom rather than on a disease, just as the clinician focuses on the chief complaint of each patient. These include cough, dyspnea, wheeze, hemoptysis, chest pain, snoring, sinigultus, sneeze, globus sensation, sore throat, halitosis, hoarseness, epistaxis, nasal obstruction, rhinorrhea, and postnasal drip. Background information on relevant anatomy and pathophysiology is presented first, followed by a discussion of the factors and diseases that can produce each symptom. A rational diagnostic approach is outlined, and options for specific treatment of the underlying causes, and nonspecific symptomatic therapy are reviewed. The discussions of nonspecific symptomatic therapies are particularly useful because these topics are largely neglected in disease-specific texts and in medical training in general.

The text is clearly written, logical, and thoroughly referenced, although some chapters are more richly developed than others. A consistent use of subheading and emphasis styles makes it relatively easy to negotiate each chapter. The illustrations are a tremendous asset. Most chapters contain a summary algorithm outlining the suggested overall clinical approach. Important points are emphasized with simple tables, diagrams, and figures. Illustrative radiographs and sharp color photographs contribute to the visual appeal of the book and are useful for clinical reference. The index is well organized with major and minor headings, but also cross-referenced. A relevant page number is listed for each entry, rather than referring the reader to a different index entry. Finally, the book is compact, printed with a clearly readable font on good quality paper, and neatly bound. I found only one minor typographical error.

I have few criticisms of the book. Detailed discussions of specific treatments for all known causes of a particular symptom seem beyond the scope of this text. In general, considerable space is devoted to disease-specific treatment recommendations that are nevertheless too superficial to be really useful (eg, the overview of the management of cystic fibrosis presented in the chapter, "Wheeze"). A reminder to pursue therapy directed at the specific cause and a brief statement of presently available therapy options would suffice. In other instances, specific therapy is directly relevant to symptom relief, offers insight into pathophysiology, and clearly warrants discussion (eg, continuous positive airway pressure for relief of dyspnea during acute asthma or chronic obstructive pulmonary disease exacerbations, although in this example, I do not agree with the proposed mechanism of action.) Unfortunately, the same running head ("Chest Pain: Diagnosis") is used for both chest pain chapters ("Pathophysiology and Differential Diagnosis" and "Diagnostic Strategies and Treatment"), resulting in unnecessary difficulty in locating the chapter of interest.

The intended readership includes a broad range of medical care providers, including nurse practitioners, medical trainees, primary care physicians, allergists, otolaryngologists, and pulmonologists. Although the book would serve as a useful reference for any clinician, I find it better suited to in-depth study than to quick reference uses because of its comprehensive and detailed approach. I think it will be most valuable as a definitive reference for specialty consultants for these reasons. Respiratory therapists may find the book useful, particularly those involved in pulmonary rehabilitation, home care, and ambulatory care. The emphasis is sensibly placed on symptoms evaluated in ambulatory care settings. The management of symptoms under special circumstances (such as the dyspnea, cough, and wheezing commonly experienced by patients undergoing mechanical ventilation) are largely absent from this otherwise comprehensive work.

In summary, this textbook is well-written, nicely illustrated, accurate, up to date, and extensively referenced. Its symptom-oriented approach is clinically practical, and the contributions of the authors have been carefully merged into a consistent, highly-readable volume. It will be useful to any clinician caring for patients with respiratory symptoms and is comprehensive and authoritative enough to be helpful to experienced specialty consultants.

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Non-Invasive Respiratory Support, Anita K Simonds MD FRCP. Editor. Soft-cover, illustrated, 173 pages. London, UK: Chapman & Hall Medical; 1996. $29.95.

The editor, who is also the primary author of 11 of the 16 chapters, is a physician at Royal Brompton Hospital. Other contributing authors are physicians and physiotherapists. The stated purpose of the book is to describe "practical aspects of nasal intermittent positive pressure ventilation, negative pressure ventilation, continuous positive airway pressure and other noninvasive respiratory support methods in adults and children." The intent of the book is to go beyond discussions of how to apply noninvasive ventilation, going on to consider when to apply the therapy and why it works. Emphasis is placed on noninvasive positive pressure ventilation since this method is more widely available.

The chapters cover a wide range of topics from general "pathophysiology of respiratory failure" to very specific "noninvasive ventilation in progressive neuromuscular disease and multiple handicaps." The more general chapters are covered in a cursory fashion and appear naïve. For example, 9 pages are devoted to the pathophysiology of ventilatory failure and 22 to noninvasive equipment. The chapters cover the gamut of patient populations from the operating theater to home care, but the organization of the chapters is a little difficult to follow. For example, some chapters are devoted to specific disease processes such as restrictive and obstructive lung diseases, while other chapters focus on particular therapies such as CPAP. Consequently, there are times the book fails to 'hang together' and reads more like individual articles than a book.

The authors provide a list of abbreviations that is helpful for the unfamiliar reader. The appendixes provide useful information, such as a list of suppliers of ventilatory equipment and a list of "useful contact addresses." It should be noted that the authors are from the United Kingdom, Ireland, and France so the focus of the book is international, although some of the information is specific to Europe. The authors have provided an index that is useful to the reader.

The real strength of the book is the clinical pearls drawn from the rich experience of the authors. For example, the authors outline various treatment options to consider before starting home ventilation and suggest techniques for starting CPAP. The book

includes other less common topics that may be helpful in managing specific patient populations, such as pregnancy and scoliosis, pediatric noninvasive ventilation, and progressive neuromuscular disease. Another helpful topic is the discussion of whether noninvasive ventilation is even appropriate for some patients.

The chapter on physiotherapy and nasal intermittent positive pressure ventilation discusses patient care from the perspective of the physiotherapist. This perspective encompasses issues that would be managed by nurses and respiratory therapists in the United States. Examples include fear and anxiety, suctioning, and pressure area care. These topics provide more clinical pearls and highlight the importance of a holistic perspective in managing patients on noninvasive ventilation. However, the information is presented so briefly that its usefulness is diminished.

The chapters are well-written and referenced. There are times when the text reads more like a review of literature than an applied handbook. Supporting data are displayed in charts and graphs. There are numerous photographs throughout the chapters, which would be of particular interest to the novice clinician.

The book has an attractive soft cover with a picture of a patient on the cover. However, the book dimensions (7.5 x 10 inches) preclude carrying in one's pocket, making the how-to information less accessible to the clinician. There are a few typographical errors. The numerous photographs and graphs have been reproduced clearly. The references are current.

In summary, the authors have achieved their goal of going beyond the *how* of noninvasive ventilation. They have provided clinically relevant information about when to apply this therapy and why it works. The audience who would benefit most from reading this book are clinicians who have little experience with noninvasive ventilation techniques and who need help to develop clinical expertise. The major limitation is the organization and coherence of the material.

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Oxygen Regulation of Ion Channels and Gene Expression, José López Barneo MD PhD and E Kenneth Weir MD, Editors. Hardcover, 352 pages. Armonk NY: Futura Publishing Co Inc; 1998. $120.00.

Exposure to hypoxia brings about rapid adjustments, such as increase in ventilation and a rise in pulmonary artery pressure, as well as longer-term reactions like causing greater erythropoietin production and greater numbers of red cells. In recent years, major advances have been made in understanding the molecular basis of these events, which are summarized in the book *Oxygen Regulation of Ion Channels and Gene Expression*. The book has its origin in an international workshop held in Madrid in December 1996, and the book chapters seem to be based largely on presentations at that meeting.

The first part of the book deals with gene expression. It is now recognized that hypoxia, even for a relatively short period of time, can induce changes in the expression of genes such as the erythropoietin, vascular endothelial growth factor, and for many of the enzymes involved in anaerobic glycolysis. A protein called 'hypoxia inducible factor' (HIF-1) seems to play a major role in gene induction, particularly for erythropoietin. HIF-1 consists of 2 proteins, HIF-alpha and HIF-1 beta, which are present even during normoxia. HIF-alpha contains cistern sulfhydryl group which remain reduced with hypoxia and facilitate HIF-1binding to the promoter regions of the erythropoietin gene. The exact mechanisms that are involved in this process are still unknown, but oxygen radicals may be involved since hydrogen peroxide depresses erythropoietin function.

The second part of the volume is concerned with the effects of hypoxia on potassium and other ion channels. The rapid adjustments to hypoxia are initiated by the secretion of neurotransmitters from the type I cells of the carotid body and the contraction of the smooth muscle of the pulmonary vasculature.

Closure of the potassium channels by hypoxia leads to cell depolarization and an increase in intracellular calcium (mainly from the extracellular fluid through L-type calcium channels). The higher intracellular calcium leads to neurotransmitter release in the carotid body and smooth muscle contraction in the pulmonary arterial system. Here also, oxygen radicals may be involved in the process, while a hemoprotein, perhaps in the potassium channel itself, actually senses the oxygen change.

The book is generally a good summary of recent hypoxia research, particularly on exciting new findings, which in the long run will lead to significant therapeutic advances. Unfortunately, like many books based on scientific meetings, the chapters are rather uneven in clarity and interest. Some describe the recent experiments of the authors and are of interest primarily to those doing research in similar areas. However, other chapters are useful summaries of current research and are of more general interest.

Many of the leading figures in research in hypoxia are contributors to this book, but there are notable investigators missing, and little attention is given to metabolic and mitochondrial theories of hypoxia sensing or to a discussion of the experimental results that form the basis of such theories. This one-sided approach diminishes the value of the book for the general reader.

Nonetheless, if you can afford the rather steep cost of the book and are willing to devote more than spare time to reading it, there are noteworthy rewards in terms of the new insights and concepts presented on oxygen lack and compensations for it.

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The Editors of RESPIRATORY CARE are deeply grateful to the following persons who have contributed their expertise and time to the reviewing of manuscripts and OPEN FORUM abstracts during the past year.

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Blue Facial Mask. SleepNet Corporation introduces its new, blue Phantom Nasal Mask. A company spokesperson explained that their consumers wanted a mask that wouldn't discolor over time. SleepNet literature says the blue mask won't discolor and that the color blue is a therapeutic sleep color that is esthetically pleasing to consumers. The company says the Phantom mask is latex free and hypoallergenic with a gel cushion that securely conforms to the patient's face, minimizing leaks. SleepNet says the mask is designed for simplicity with a built-in exhalation port, an additional port for supplemental oxygen or pressure measurement, and easy-to use headgear with an integrated tube and swivel to direct tubing away from the patient's field of vision. For more information from SleepNet, circle number 174 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Monitoring System with Patient Alarm. Protocol Systems Inc recently announced it has added to its Flexible Monitoring System the Data Critical StatView Patient Alarm Notification capability. According to a company press release, StatView™, manufactured by Data Critical Corp of Redmond, Washington, provides caregivers wireless wide-area patient alarm notification and vital signs from Protocol's Flexible Monitoring® network. Protocol Systems explains that StatView acquires patient alarm and vital signs data remotely from Protocol's Acuity® central monitoring workstation and displays it on a hand-held device carried by the clinician. The company says that within 10 seconds of a patient alarm, StatView will display the six-second electrocardiography waveform representing the data that caused the alarm along with the patient's name and location. For more information from Protocol Systems, circle number 175 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

New Generic Drug. Roxane Laboratories Inc has announced the introduction of the first generic of Hydromorphone HCl 8 mg tablets CII USP. Roxane says the new product is available immediately along with its previous line including 2 mg and 4 mg tablets in bottles of 100 and reverse numbered blister packs of 25 tablets and 1 mg/mL oral solution in 120 mL, 250 mL and 500 mL bottles and 4 mL x 40 Unit Dose Patient Cups™, and 8 mL x 40 Unit Dose Patient Cups. For more information from Roxane Laboratories, circle number 176 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Online Medical Dictionary. FA Davis Company recently introduced Taber's Online, an online service available at www.tabers.com. A company press release says the entire contents of Taber's Cyclopedic Medical Dictionary, 18th Edition, will be available as a subscription service on the World Wide Web. The company says the service includes the 55,000 full-length definitions from Taber's and features pronunciations (many with audio files), illustrations, photographs, tables, etymologies, abbreviations, and synonyms. Where applicable, FA Davis literature says, the definitions also include the cyclopedic information that sets Taber's apart from other health science dictionaries. The company says, most web browsers will be able to access Taber's Online, but note that the latest versions of Netscape and MS Internet Explorer are recommended for optimum performance. For more information from FA Davis circle number 177 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

New Medication Delivery System. Glaxo Wellcome announced recently that the US Food and Drug Administration cleared Serevent® Diskus® (salmeterol xinafoate inhalation powder) for use in children with asthma as young as 4 years of age. The company says the product is available for the maintenance treatment of asthma in children 4 years of age and older who have reversible obstructive airway disease, including nocturnal symptoms. Glaxo Wellcome also says the product has been approved for the prevention of exercise-induced bronchospasm in both children and adults. For more information from Glaxo Wellcome, circle number 178 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ____ of ____

Form Approved: OMB No. 0910-0291 Expires: 4/30/96
See OMB statement on reverse

FDA Use Only (Resp Care)

Triage unit sequence #

A. Patient information

1. Patient identifier / In confidence

2. Age at time of event: or Date of birth:

3. Sex: ☐ female ☐ male

4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

☐ death ____ (mo/day/yr)
☐ life-threatening
☐ hospitalization – initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: ____

3. Date of event (mo/day/yr)

4. Date of this report (mo/day/yr)

5. Describe event or problem

Relevant tests/laboratory data, including dates

Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1
#2

2. Dose, frequency & route used
#1
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1
#2

4. Diagnosis for use (indication)
#1
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
– –

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
☐ health professional
☐ lay user/patient
☐ other: ____

5. Expiration date (mo/day/yr)

6.
model # ____
catalog # ____
serial # ____
lot # ____
other # ____

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address

phone #

2. Health professional? ☐ yes ☐ no

3. Occupation

4. Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

FDA Form 3500 1/96)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling
- therapeutic failures

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

- 1-800-FDA-0178 to FAX report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 to report by phone or for more information
- 1-800-822-7967 for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

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FDA Form 3500-back

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The FDA Medical Products Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

American Association for Respiratory Care

MEMBERSHIP APPLICATION

Please read the eligibility requirements for each of the classifications in the right-hand column, then complete the applicable section. All information requested below must be provided, except where indicated as optional. See other side for more information and fee schedule. Please sign and date application an reverse side and type or print clearly. Processing of application takes approximately 15 days.

- ☐ Active
- Associate
  - ☐ Foreign
  - ☐ Physician
  - ☐ Industrial
- ☐ Special
- ☐ Student

Last Name _____

First Name _____

Social Security No. _____

Home Address _____

City _____

State _____ Zip __ __ __ __ __ — __ __ __ __

Phone No. (_____) _____

Primary Job Responsibility (check one only)

- ☐ Technical Director
- ☐ Assistant Technical Director
- ☐ Pulmonary Function Specialist
- ☐ Instructor/Educator
- ☐ Supervisor
- ☐ Staff Therapist
- ☐ Staff Technician
- ☐ Rehabilitation/Home Care
- ☐ Medical Director
- ☐ Sales
- ☐ Student
- ☐ Other, specify _____

Type of Business

- ☐ Hospital
- ☐ Skilled Nursing Facility
- ☐ DME/HME
- ☐ Home Health Agency
- ☐ Educational Institution
- ☐ Manufacturer or supplier
- ☐ Other, specify _____

Date of Birth (optional) _____ Sex (optional) _____

U.S. Citizen? ____ Yes ____ No

Have you ever been a member of the AARC? _____

If so, when? From _____ to _____

Preferred mailing address: ☐ Home ☐ Business

For office use only

FOR ACTIVE MEMBER

An individual is eligible if he/she lives in the U.S. or its territories or was an Active Member prior to moving outside its borders or territories, and meets ONE of the following criteria: (1) is legally credentialed as a respiratory care professional if employed in a state that mandates such, OR (2) is a graduate of an accredited educational program in respiratory care, OR (3) holds a credential issued by the NBRC. An individual who is an AARC Active Member in good standing on December 8, 1994, will continue as such provided his/her membership remains in good standing

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE.

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FOR ASSOCIATE OR SPECIAL MEMBER

Individuals who hold a position related to respiratory care but do not meet the requirements of Active Member shall be Associate Members. They have all the rights and benefits of the Association except to hold office, vote, or serve as chair of a standing committee. The following subclasses of Associate Membership are available: Foreign, Physician, and Industrial (individuals whose primary occupation is directly or indirectly devoted to the manufacture, sale, or distribution of respiratory care equipment or supplies). Special Members are those not working in a respiratory care-related field

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE

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FOR STUDENT MEMBER

Individuals will be classified as Student Members if they meet all the requirements for Associate Membership and are enrolled in an educational program in respiratory care accredited by, or in the process of seeking accreditation from, an AARC-recognized agency

SPECIAL NOTICE — Student Members do not receive Continuing Respiratory Care Education (CRCE) transcripts. Upon completion of your respiratory care education, continuing education credits may be pursued upon your reclassification to Active or Associate Member

School/RC Program _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

Length of program

☐ 1 year ☐ 4 years
☐ 2 years ☐ Other, specify _____

Expected Date of Graduation *(REQUIRED INFORMATION)*

Month _____ Year _____

Demographic Questions

We request thot you answer these questions in order to help us design services and progroms to meet your needs.

Check the Highest Degree Earned

- ☐ High School
- ☐ RC Graduote Technician
- ☐ Associate Degree
- ☐ Bachelor's Degree
- ☐ Master's Degree
- ☐ Doctorote Degree

Number of Years in Respiratory Care

- ☐ 0-2 years
- ☐ 3-5 years
- ☐ 6-10 years
- ☐ 11-15 Years
- ☐ 16 years ar more

Job Status

- ☐ Full Time
- ☐ Port Time

Credentials

- ☐ RRT
- ☐ CRTT
- ☐ Physician
- ☐ CRNA
- ☐ RN
- ☐ LVN/LPN
- ☐ CPFT
- ☐ RPFT
- ☐ Perinatal/Pediatric

Salary

- ☐ Less than $10,000
- ☐ $10,001-$20,000
- ☐ $20,001-$30,000
- ☐ $30,001-$40,000
- ☐ $40,000 or mare

PLEASE SIGN

I hereby apply for membership in the American Association for Respiratory Care and have enclased my dues If appraved for membership in the AARC, I will abide by its bylaws and profeссional code of ethics. I authorize investigation of all statements contained herein and understand that misrepresentations ar amissions of facts called for is cause for rejection ar expulsion.

A yearly subscription to RESPIRATORY CARE journal and *AARC Times* magazine includes an allocation af $11.50 from my dues far each of these publications

NOTE Contributians ar gifts to the AARC are nat tax deductible as charitable contributions for income tax purposes However, they may be tax deductible as ordinary and necessary business expenses subject to restrictions imposed as a result af association lobbying activities The AARC estimates that the nondeductible partian af yaur dues — the portion which is allocable to labbying — is 26%.

Signature _____

Date _____

Membership Fees

Payment must accompony your opplicotion to the AARC. Fees are for 12 months. (NOTE: Renewal fees ore $75.00 Active, Associote-Industrial ar Associote-Physician, or Special status; $90.00 for Associote-Foreign status; ond $45.00 for Student status).

☐ Active	$ 87.50
☐ Associate (Industrial or Physician)	$ 87.50
☐ Associate (Foreign)	$102.50
☐ Special	$ 87.50
☐ Student	$ 45.00
TOTAL	$_____

Specialty Sections

Established to recognize the speciolty oreos of respirotory care, these sections publish o bi-monthly newsletter thot focuses on issues of specific concern to thot specialty. The sections olso design the specialty programming ot the nationol AARC meetings.

☐ Adult Acute Core Section	$15.00
☐ Education Section	$20.00
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☐ Continuing Core-Rehabilitation Section	$15.00
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☐ Transport Section	$15.00
☐ Home Care Section	$15.00
☐ Subacute Care Section	$15.00
TOTAL	$_____

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call for abstracts

1999 RESPIRATORY CARE OPEN FORUM

The American Association for Respiratory Care and its science journal, RESPIRATORY CARE, invite submission of brief abstracts related to any aspect of cardiorespiratory care. The abstracts will be reviewed, and selected authors will be invited to present posters at the OPEN FORUM during the AARC International Respiratory Congress in Las Vegas, Nevada, December 13–16, 1999. Accepted abstracts will be published in the November 1999 issue of RESPIRATORY CARE. Membership in the AARC is not required for participation. All accepted abstracts are automatically considered for ARCF research grants.

SPECIFICATIONS—READ CAREFULLY!

An abstract may report **(1) an original study, (2) the evaluation of a method, device or protocol, or (3) a case or case series.** Topics may be aspects of adult acute care, continuing care/rehabilitation, perinatology/pediatrics, cardiopulmonary technology, or health care delivery. The abstract may have been presented previously at a local or regional—but not national—meeting and should not have been published previously in a national journal. The abstract is the only evidence by which the reviewers can decide whether the author should be invited to present a poster at the OPEN FORUM. Therefore, *the abstract must provide all important data, findings, and conclusions.* Give specific information. Do not write general statements, such as "Results will be presented" or "Significance will be discussed."

ESSENTIAL CONTENT ELEMENTS

Original study. Abstract *must* include (1) Background: statement of research problem, question, or hypothesis; (2) Method: description of research design and conduct in sufficient detail to permit judgment of validity; (3) Results: statement of research findings with quantitative data and statistical analysis; (4) Conclusions: interpretation of the meaning of the results.

Method, device, or protocol evaluation. Abstract *must* include (1) Background: identification of the method, device, or protocol and its intended function; (2) Method: description of the evaluation in sufficient detail to permit judgment of its objectivity and validity; (3) Results: findings of the evaluation; (4) Experience: summary of the author's practical experience or a lack of experience; (5) Conclusions: interpretation of the evaluation and experience. Cost comparisons should be included where possible and appropriate.

Case report. Abstract *must* report a case that is uncommon or of exceptional educational value and must include (1) Introduction: relevant basic information important to understanding the case. (2) Case Summary: patient data and response, details of interventions. (3) Discussion: content should reflect results of literature review. The author(s) should have been actively involved in the case and a case-managing physician must be a co-author or must approve the report.

FORMAT AND TYPING INSTRUCTIONS

Accepted abstracts will be photographed and reduced by 40%; therefore, the size of the original text should be *at least* 10 points. *Abstracts should be 400 words or less and may have 1 clear, concise table or figure.* A font like Helvetica or Geneva makes the clearest reproduction. The first line of the abstract should be the title in all capital letters. Title should explain content. Follow title with names of all authors (including credentials), institution(s), and location; underline presenter's name. Type or electronically print the abstract *single spaced in a single paragraph in the space provided on the abstract blank.* Insert only one letter space between sentences. Text submission on diskette is encouraged but must be accompanied by a hard copy. *Data may be submitted in table form, or a simple figure may be included provided it fits within the space allotted. No figure, illustration, or table is to be attached to the abstract form.* Provide all author information requested. A clear photocopy of the abstract form may be used. Standard abbreviations may be employed without explanation; new or infrequently used abbreviations should be spelled out on first use. Any recurring phrase or expression may be abbreviated, if it is first explained. Check the abstract for (1) errors in spelling, grammar, facts, and figures; (2) clarity of language; and (3) conformance to these specifications. An abstract not prepared as requested may not be reviewed. Questions about abstract preparation may be telephoned to the editorial staff of RESPIRATORY CARE at (972) 406-4667.

Early Deadline Allowing Revision. Authors may choose to submit abstracts early. Abstracts postmarked by April 2, 1999 will be reviewed and the authors notified *by letter only* to be mailed by May 7, 1999. Rejected abstracts will be accompanied by a written critique that should, in many cases, enable authors to revise their abstracts and resubmit them by the Final Deadline (June 11, 1999).

Final Deadline. The mandatory Final Deadline is June 11, 1999 (postmark). Authors will be notified of acceptance or rejection *by letter only*. These letters will be mailed by August 25, 1999.

Mailing Instructions. Mail (do not fax!) 2 clear copies of the completed abstract form, diskette (if possible), and a stamped, self-addressed postcard (for notice of receipt) to:

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1999 Respiratory Care Open Forum Abstract Form

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4. **Do not use type size less than 10 points.** (Do not exceed 400 words.)
5. All text and the table, or figure, must fit into the rectangle shown. (Use only 1 clear, concise table or figure.)
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Manuscript Preparation Guide

General Information

RESPIRATORY CARE welcomes original manuscripts related to the science and technology of respiratory care and prepared according to these Instructions and the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* [Respir Care 1997; 42(6):623-634]. Manuscripts are blinded and reviewed by professionals who are experts in their fields. Authors are responsible for all aspects of the manuscript and receive galleys to proofread before publication. Each accepted manuscript is copyedited so that its message is clear and it conforms to the Journal's style. Published papers are copyrighted by Daedalus Inc and may not be published elsewhere without permission.

Editorial consultation is available at any stage of planning or writing. On request, specific guidance is provided for all publication categories. To receive these Instructions and related materials, write to RESPIRATORY CARE, 600 Ninth Avenue, Suite 702, Seattle WA 98104, call (206) 223-0558, or fax (206) 223-0563.

Publication Categories & Structure

Research Article: A report of an original investigation (a study). It includes a Title Page, Abstract, Introduction, Methods, Results, Discussion, Conclusions, Product Sources, Acknowledgments, References, Tables, Appendices, Figures, and Figure Captions.

Evaluation of Device/Method/Technique: A description and evaluation of an old or new device, method, technique, or modification. It has a Title Page, Abstract, Introduction, Description of Device/Method/Technique, Evaluation Methods, Evaluation Results, Discussion, Conclusions, Product Sources, Acknowledgments, References, Tables, Appendices, Figures, and Figure Captions. Comparative cost data should be included wherever possible.

Case Report: A report of a clinical case that is uncommon, or was managed in a new way, or is exceptionally instructive. All authors must be associated with the case. A case-managing physician must either be an author or furnish a letter approving the manuscript. Its components are Title Page, Abstract, Introduction, Case Summary, Discussion, References, Tables, Figures, and Figure Captions.

Review Article: A comprehensive, critical review of the literature and state-of-the-art summary of a pertinent topic that has been the subject of at least 40 published research articles. Title Page, Outline, Introduction, Review of the Literature, Summary, Acknowledgments, References, Tables, Appendices, and Figures and Captions may be included.

Overview: A critical review of a pertinent topic that has fewer than 40 published research articles.

Update: A report of subsequent developments in a topic that has been critically reviewed in this Journal or elsewhere.

Point-of-View Paper: A paper expressing personal but substantiated opinions on a pertinent topic. Title Page, Text, References, Tables, and Illustrations may be included.

Special Article: A pertinent paper not fitting one of the foregoing categories may be acceptable as a Special Article. Consult with the Editor before writing or submitting such a paper.

Editorial: A paper drawing attention to a pertinent concern; it may present an opposing opinion, clarify a position, or bring a problem into focus.

Letter: A signed communication, marked "For publication," about prior publications in this Journal or about other pertinent topics. Tables and illustrations may be included.

Blood Gas Corner: A brief, instructive case report involving blood gas values—with Questions, Answers, and Discussion.

Drug Capsule: A mini-review paper about a drug or class of drugs that includes discussions of pharmacology, pharmacokinetics, and pharmacotherapy.

Graphics Corner: A brief case report incorporating waveforms for monitoring or diagnosis—with Questions, Answers, and Discussion.

Kittredge's Corner: A brief description of the operation of respiratory care equipment—with information from manufacturers and editorial comments and suggestions.

PFT Corner: Like Blood Gas Corner, but involving pulmonary function tests.

Cardiorespiratory Interactions. A case report demonstrating the interaction between the cardiovascular and respiratory systems. It should be a patient-care scenario; however, the case—the central theme—is the systems interaction. CRI is characterized by figures, equations, and a glossary. See the March 1996 Issue of RESPIRATORY CARE for more detail.

Test Your Radiologic Skill: Like Blood Gas Corner, but involving pulmonary medicine radiography and including one or more radiographs; may involve imaging techniques other than conventional chest radiography.

Review of Book, Film, Tape, or Software: A balanced, critical review of a recent release.

Preparing the Manuscript

Print on one side of white bond paper, 8.5 in. x 11 in. (216 x 279 mm) with margins of at least 1 in. (25 mm) on all sides of the page. Use ***double-spacing*** throughout the ***entire*** manuscript. Use a standard font (eg, Times, Helvetica, or Courier) at least 10 points in size, and

do not use italics except for special emphasis. Number all pages in upper-right corners. Indent paragraphs 5 spaces. Do ***not justify***. **Do *not* put authors' names, institutional affiliations or allusions to institutional affiliations in the text, or other identification anywhere except on the title page.** Repeat title only (no authors) on the abstract page. Begin each of the following on a new page: Title Page, Abstract, Text, Product Sources List, Acknowledgments, References, each Table, and each Appendix. Use standard English in the first person and active voice.

Center main section headings on the page and type them in capital and small letters (eg, Introduction, Methods, Results, Discussion). Begin subheadings at the left margin and type them in capital and small letters (eg, Patients, Equipment, Statistical Analysis).

References. Cite only published works as references. Manuscripts accepted but not yet published may be cited as references: designate the accepting journal, followed by (in press), and provide 3 copies of the in-press article for reviewer inspection. Cite references in the text with superscript numerals. Assign numbers in the order that references are first cited. On the reference page, list the cited works in numerical order. Follow the Journal's style for references. Abbreviate journal names as in *Index Medicus*. List all authors.

Article in a journal carrying pagination throughout volume:

> Rau JL, Harwood RJ. Comparison of nebulizer delivery methods through a neonatal endotracheal tube: a bench study. Respir Care 1992;37(11):1233-1240.

Article in a publication that numbers each issue beginning with Page 1:

> Bunch D. Establishing a national database for home care. AARC Times 1991;15(Mar):61,62,64.

Corporate author journal article:

> American Association for Respiratory Care. Criteria for establishing units for chronic ventilator-dependent patients in hospitals. Respir Care 1988;33(11):1044-1046.

Article in journal supplement: (Journals differ in their methods of numbering and identifying supplements. Supply sufficient information to promote retrieval.)

> Reynolds HY. Idiopathic interstitial pulmonary fibrosis. Chest 1986; 89(3 Suppl):139S-143S.

Abstract in journal: (Abstracts citations are to be avoided. Those more than 3 years old should not be cited.)

> Stevens DP. Scavenging ribavirin from an oxygen hood to reduce environmental exposure (abstract). Respir Care 1990;35(11): 1087-1088.

Editorial in journal:

> Enright P. Can we relax during spirometry? (editorial). Am Rev Respir Dis 1993;148(2):274.

Editorial with no author given:

> Negative-pressure ventilation for chronic obstructive pulmonary disease (editorial). Lancet 1992;340(8833):1430-1441.

Letter in journal:

> Aelony Y. Ethnic norms for pulmonary function tests (letter). Chest 1991;99(4):1051.

Paper accepted but not yet published:

> Hess D. New therapies for asthma. Respir Care (year, in press).

Personal author book: (For any book, specific pages should be cited whenever possible.)

> DeRemee RA. Clinical profiles of diffuse interstitial pulmonary disease. New York: Futura; 1990. p. 76-85.

Corporate author book:

> American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group; 1977.

Chapter in book with editor(s):

> Pierce AK. Acute respiratory failure. In: Guenter CA, Welch MH, editors. Pulmonary medicine. Philadelphia: JB Lippincott; 1977:26-42.

Tables. Use consecutively numbered tables to display information. Start each table on a separate page. Number and title the table and give each column a brief heading. Place explanations in footnotes, including all nonstandard abbreviations and symbols. Key the footnotes with conventional designations (*, †, ‡, §, ‖, ¶, **, ††) in consistent order, placing them superscript in the table body. Do not use horizontal or vertical rules or borders. Do not submit tables as photographs, reduced in size, or on oversize paper. Use the same typeface as in the text.

Illustrations. Graphs, line drawings, photographs, and radiographs are figures. Use only illustrations that clarify and augment the text. Number them consecutively as Fig. 1, Fig. 2, and so forth according to the order by which they are mentioned in the text. Be sure all figures are cited. If any figure was previously published, include copyright holder's written permission to reproduce. Figures for publication must be of professional quality. Data for the original graphs should be available to the Editor upon request. If color is essential, consult the Editor for more information. In reports of animal experiments, use schematic drawings, not photographs. A letter of consent must accompany any photograph of a person. Do not place titles and detailed explanations on figures; put this information in figure captions. If possible, submit radiographs as prints and full-size copies of film.

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Ethics. When reporting experiments on human subjects, indicate that procedures were conducted in accordance with the ethical standards of the *World Medical Association Declaration of Helsinki* [Respir Care 1997;42(6):635-636] or of the institution's committee

on human experimentation. State that informed consent was obtained. Do not use patient's names, initials, or hospital numbers in text or illustrations. When reporting experiments on animals, indicate that the institution's policy, a national guideline, or a law on the care and use of laboratory animals was followed.

Statistics. Identify the statistical tests used in analyzing the data, and give the prospectively determined level of significance in the Methods section. Report actual p values in Results. Cite only textbook and published article references to support choices of tests. Identify any general-use or commercial computer programs used, naming manufacturers and their locations. These should be listed on the product-sources page.

Units of Measurement. Express measurements of length, height, weight, and volume in metric units appropriately abbreviated; temperatures in degrees Celsius; and blood pressures in millimeters of mercury (mm Hg). Report hematologic and clinical-chemistry measurements in conventional metric and in SI (*Systémé Internationale*) units. Show gas pressures (including blood gas tensions) in torr. List SI equivalent values, when possible, in brackets following non-SI values—for example, "PEEP, 10 cm H_2O [0.981 kPa]." For conversion to SI, see RESPIRATORY CARE 1988;33(10):861-873 (Oct 1988), 1989;34(2):145 (Feb 1989), and 1997;42(6):639-640 (June 1997).

Conflict of Interest. Authors are asked to disclose any liaison or financial arrangement they have with a manufacturer or distributor whose product is part of the submitted manuscript or with the manufacturer or distributor of a competing product. (Such arrangements do not disqualify a paper from consideration and are not disclosed to reviewers.) A statement to this effect is included on the cover-letter page. (Reviewers are screened for possible conflict of interest.)

Abbreviations and Symbols. Use standard abbreviations and symbols. Avoid creating new abbreviations. Avoid all abbreviations in the title and unusual abbreviations in the abstract. Use an abbreviation only if the term occurs several times in the paper. Write out the full term the first time it appears, followed by the abbreviation in parentheses. Thereafter, employ the abbreviation alone. Never use an abbreviation without defining it. Standard units of measurement can be abbreviated without explanation (eg, 10 L/min, 15 torr, 2.3 kPa).

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Submitting the Manuscript

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Has this research received any grants or other support, financial or material? ❑ Yes ❑ No

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AARC & AFFILIATES

January 29-30, 1999—*San Antonio, Texas*
The AARC and the University of Texas Health Science Center of San Antonio are presenting a post-graduate short course on Disease Management: Astham and COPD. The program will allow the practitioner to gain the skills and information necessary to design and implement programs in the disease management of asthma and/or COPD. Fourteen hours of CRCE credit will be offered. The two-day Seminar will be held at the Hilton San Antonio Airport.
Contact: (972) 243-2272

February 10-12, 1999—*Clackamas, Oregon*
The OSRC presents its annual Pacific Northwest Respiratory Care Conference at the Monarch Hotel and Conference Center. Topics include respiratory mechanics, optimal humidification, smoking cessation, airway obstruction in children, ethical dilemmas, and COPD drug therapy.
Contact: Irene Iwata-Morgan, RRT at (503) 494-6158

April 7-9, 1999—*Gulf Shores, Alabama*
The Alabama Society for Respiratory Care will be hosting their state educational meeting at the Gulf State Park Resort Hotel and Convention Center.
Contact: David Howard (205) 761-4573 or e-mail William.Howard@bhsala.com.

April 13-14, 1999—*King of Prussia, Pennsylvania*
The PSRC will host their 2nd Annual Eastern Regional Conference & Exhibition at the Holiday Inn. Guest speakers include Sam Giordano, MBA, RRT, and Richard Branson, BA, RRT.
Contact: Angie Herstine (609) 784-0340

April 23-25, 1999—*Kingsport, Tennessee*
The TSRC presents its annual convention and exhibition, The New Millennium: Somewhere Over the Rainbow, at the Meadowview Resort and Convention Center. Topics will include clinical, management, patient assessment, and student issues. 13 contact hours are available.
Contact: Colleen Schabacker (615) 384-1731

Other Meetings

January 21-23—*Washington, DC*
The AARC is cosponsoring Health Action '99: Putting the Pieces Together. This national grassroots conference of health advocates will be held at the Renaissance Mayflower Hotel. Topics include Medicare, children's health insurance, managed care reforms, and universal coverage.
Contact: Families USA at (202) 628-3030, info@familiesusa.org, or www.familiesusa.org

February 7-10, 1999—*Whistler, British Columbia, Canada*
The American College of Chest Physicians is sponsoring a Cardiopulmonary Wellness and Rehabilitation meeting at the Chateau Whistler Resort.
Contact: ACCP Member Services at (800) 343-2227 or (847) 498-1400.

February 13-20, 1999—*St. Moritz, Switzerland*
The Seventh Winter Symposium on Intensive Care Medicine will be held in St. Moritz and is jointly sponsored by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine (USA).
Contact: Ana Maria de Campos at 32.2 555 3215 or e-mail sympicu@resulb.ulb.ac.be.

February 21-25—*Keystone, Colorado*
The Children's National Medical Center presents their 15th Annual CNMC Symposium on ECMO and Advanced Therapies for Respiratory Failure at the Keystone Resort. Topics include nitric oxide, neonatal pulmonary support, and liquid ventilation. CME, CEU, CRCE and perfusion recertification credit available.
Contact: ECMO at (202) 884-5018

March 14-17—*Orlando, Florida*
Noninvasive Ventialtion, the seventh international conference of the American College of Chest Physicians, Independent Ventilator Users Network, and the AARC, is scheduled for the Caribe Royale Resort Suites. Topics include noninvasive ventilatory assistance in the home, ICU, ER, and long-term care sites; nutritional issues for ventilated patients; diagnosis and diagnostic methods; ethical issues; and telemonitoring in the home. Continuing education credits available.
Contact: (800) 343-2227

March 16-19, 1999—*Brussels, Belgium*
The 19th International Symposium on Intensive Care and Emergency Medicine will be head at the Congress Center in Brussels.
Contact: Ana Maria de Campos at 32.2 555 3215 or e-mail sympicu@resulb.ulb.ac.be.

April 20-23—*Clearwater Beach, Florida*
All Children's Hospital of St. Petersburg, FL, will host their 1999 Neonatal/Pediatric Transport Conference at the Hilton Clearwater Beach Resort. The conference, titled Redefining State of the Art, includes a pre-conference lab and offers 23 CEUs.
Contact: Connie Spadaccino at (727) 892-4240 or (800) 456-4543, ext. 4240.

June 12-16, 1999—*International Society for Aerosols in Medicine*
12th International Congress at the Austria Center in Vienna, Austria. Topics include aerosol drug delivery, aerosol deposition and clearance, cellular and molecular interactions, environmental aerosols, standardization, aerosol diagnostics, and aerosol therapy.
Contact: Vienna Academy of Postgraduate Medical Education and Research. Alser Strasse 4, A-1090 Vienna, Austria. Phone (+43/1) 405 13 83-22, fax (+43/1) 405 13 83-23, e-mail medacad@via.at.

Notices

Notices of competitions, scholarships, fellowships, examination dates, new educational programs, and the like will be listed here free of charge. Items for the Notices section must reach the Journal 60 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc). Include all pertinent information and mail notices to RESPIRATORY CARE Notices Dept, 11030 Ables Lane, Dallas TX 75229-4593.

Helpful Web Sites

American Association for Respiratory Care
http://www.aarc.org
— Current job listings
— American Respiratory Care Foundation fellowships, grants, & awards
— Clinical Practice Guidelines

National Board for Respiratory Care
http://www.nbrc.org

RESPIRATORY CARE online
http://www.rcjournal.com
— 1997 Subject and Author Indexes
— Contact the editorial staff

Asthma Management Model System
http://www.nhlbi.nih.gov

The National Board for Respiratory Care—1999 Examination Dates and Fees

Examination	Examination Date	Examination Fee
CRT Examination	March 13, 1999	$120 (new applicant)
	Application Deadline: January 1, 1999	80 (reapplicant)
RRT Examination	June 5, 1999	120 written only (new applicant)
	Application Deadline: February 1, 1999	80 written only (reapplicant)
CPFT Examination	June 5, 1999	130 (new applicant)
	Application Deadline. April 1, 1999	150 (reapplicant)

For information about other services or fees, write to the National Board for Respiratory Care, 8310 Nieman Road, Lenexa KS 66214, or call (913) 599-4200, FAX (913) 541-0156,or e-mail: nbrc-info@nbrc.org

WATCH FOR SPECIAL ISSUES OF RESPIRATORY CARE

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MARCH 1999

In this issue
1999 Call For Abstracts
See page 1119

New *Federal Register* Notices Now Available

The Center for Devices and Radiological Health announces the publication of new Facts-on-Demand FOD notices in the *Federal Register*. The new publications: FOD#774—Medical Devices; Preemption of State Product Liability Claims; Proposed Rule; FOD#607—Rebuilders, Reconditioners, Services, and "As Is" Remarketers of Medical Devices; Review and Revision of Compliance Policy Guides and Regulatory Requirements; Request for Comments and Information; Proposed Rule; and FOD#513—Medical Devices; Reports of Corrections and Removals; Stay of Effective Date of Information Collection Requirements; Stay of Effective Date of Final Regulation. For more information about Facts-on-Demand call (800) 899-0381 or (301) 826-0111. The FOD system is also on the Internet at w.fda.gov/cdrh/fedregin.html.

Web Site Link to Fellowships, Scholarships, & Grants

The American Association for Respiratory Care's web site contains important information about fellowships, scholarships, and research grants. International fellowships, education scholarships, research fellowships, and other grand programs are described in detail. The site also contains information about the $1,000,000 Research Fund, a restricted fund to sponsor research initiatives that document the clinical and economic impact of respiratory care professionals in the delivery of health care. To apply, a "Research Plan Abstract" must be submitted to the AARC by February 1, 1999. To find out more about these programs, log on at **www.aarc.org.**

AARC, Affiliates Set Conference Schedules

The AARC and many of the affiliates have set their schedules for 1999 conferences and seminars. Foremost among AARC's offerings are its Summer Forum (July 16-18) and Annual International Respiratory Congress (Dec. 13-16). Additionally, the AARC will be co-sponsoring the 7th International Conference on Non-invasive Ventilation on March 14-17, 1999 in Orlando. Check out the AARC's website at www.aarc.org for all meeting registration materials and a list of affiliate conferences.

Videoconference Program Set; Nursing CEUs Offered

A series of eight videoconferences are scheduled for 1999 through the AARC Professor's Rounds series, which are now approved for nursing CEUs as well as CRCE credit. Topics are: respiratory assessment, asthma management, ventilator management, disease management, pediatric emergencies, COPD, PEEP, and respiratory pharmacology.

CRCE Online Debuts

Now you can earn continuing education on the Internet from the AARC through its new CRCE Online website. After you pay for the number of continuing education units you wish to attempt (by submitting your credit card number on a secure server site), you are given access to the list of courses. Read the material, take the test, and then print out a certificate showing you passed. Your participation will also be noted on your CRCE record with the AARC. Log on to the AARC's website at www.aarc.org and look for CRCE Online.

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